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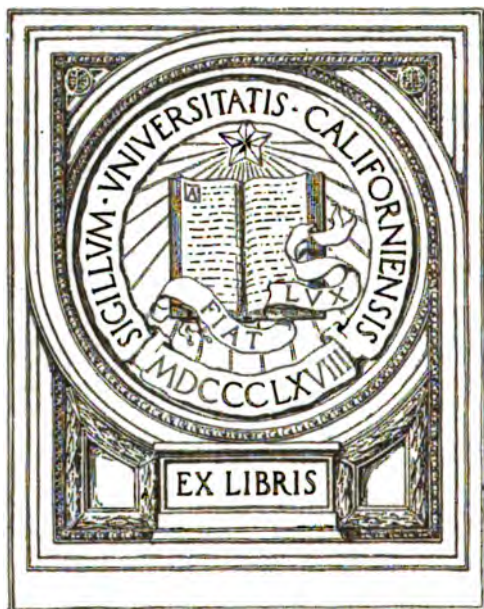
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## ALIMENTARY CANAL



# A STUDY OF THE ARTERIES SUPPLYING THE STOMACH AND DUODENUM AND THEIR RELATION TO ULCER\*

T. B. REEVES

This work was undertaken to determine, if possible, whether there is any difference in the character of the arteries in the stomach and duodenum, in the regions in which ulcers are prone to occur. At the operating table practically all ulcers of the stomach are found along the lesser curvature, and 98 per cent of the duodenal ulcers are found within one and one-half inches of the pylorus; the greater number on the anterior wall within the first inch. It would seem that there must be a special factor to cause this curiously selective character.

The two portions of the bowel, the stomach, and the first one and one-half inches of the duodenum should be considered as modified portions of the same region of the primitive alimentary tube. From an embryologic standpoint the beginning of the duodenum resembles the stomach in that it arises from the foregut. The first inch is freely movable; it is covered in front and behind by the same two layers of peritoneum that cover the stomach. The mucous surface of the first one and one-half inches of the duodenum is devoid of folds (*valvulae conniventes*) and the villi are short. The distribution of blood vessels supplying the stomach and the first one and one-half inches of the duodenum is not regular as it is in the rest of the bowel.

## TECHNIC

Sixty-two human stomachs and duodenums procured at necropsies from one to four hours after death have been investigated. Most of the specimens were injected before being removed from the body. For injecting the arteries, slightly acid gelatin-carmin solution gave the best results. Ten per cent gelatin solution was filtered through several thicknesses of cheese cloth. Sufficient carmin to make 1.5 per cent solution was ground in a mortar and partially dissolved in a

\* Reprinted from *Surg., Gynec. and Obst.* 1920, xxx, 374-385.

small amount of water containing a few drops of acetic acid; this was added to the warm gelatin solution and thoroughly stirred. A few crystals of thymol were added as a preservative. When ready for use the gelatin-carmin was melted over a water bath and injected at a temperature between 45°C. and 50°C. To inject the capillaries the carmin should first be dissolved in ammonium hydroxid to get rid of the granules, then neutralized with acetic acid (Bayne-Jones). If the gelatin-carmin solution is alkaline, the dye will diffuse through the tissue and obscure smaller vessels.

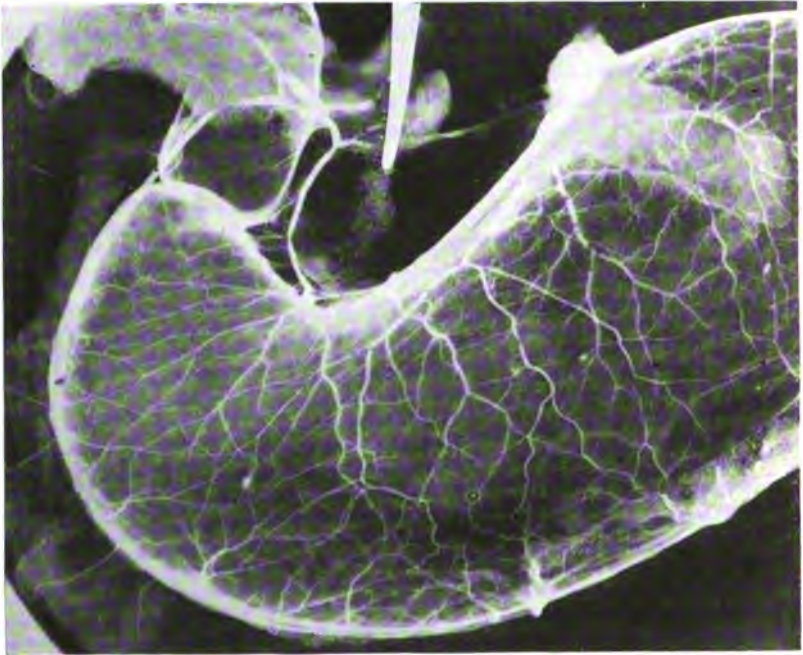


FIG. 1.—Stereoscopic roentgenogram. Vessels injected with gelatin-bismuth solution.

All of my injections were made through the celiac axis, the hepatic artery being ligated at the porta hepatis, and the inferior pancreaticoduodenal at its origin from the superior mesenteric. In some of the cases the splenic artery was clamped off at the hilus of the spleen.

Several injections were made to include the capillaries but no attempt was made to inject the veins, although they were partially filled in a few instances. As a rule the best injections were in stomachs that were moderately distended either with air or fluid. Specimens

distended with air soon after injection were useful when hardened and dried. Fixation of specimens in 10 per cent formalin solution for twelve to twenty-four hours immediately after injection proved the most instructive method as it was then comparatively easy to make a complete dissection of the vessels of the submucosa by means of a dissecting microscope. For microscopic study, blocks of tissue were cut from various parts of the stomach and duodenum and fixed in 10 per cent formalin. Serial frozen sections from 50 to 100 microns were cut, stained with hematoxylin and mounted in balsam.

A few specimens were injected with 10 per cent gelatin to which was added bismuth or barium sulphate. One specimen was injected with 15 per cent thorium and one with 25 per cent sodium bromid. Each of these specimens was distended with air and stereoscopic roentgenograms taken. The one containing barium or bismuth made the best roentgenograms (Fig. 1), but since they showed only the larger vessels in the submucosa, they were of little value in this study.

#### THE GASTRIC ARTERIAL SYSTEM

It may be well to describe briefly the larger vessels supplying the stomach and the duodenum, although my chief interest in this study was in the smaller vessels of the mucosa and submucosa of those areas of the stomach and duodenum in which ulcer is most often found.

#### THE CELIAC AXIS

The celiac axis (*arteria coeliaca*) is given off from the anterior surface of the aorta between the crura of the diaphragm a short distance below the aortic opening. It is a short, thick trunk, extends forward and slightly downward above the upper margin of the pancreas for about one-half inch, and then breaks up simultaneously just behind the posterior layer of the lesser sac of peritoneum into the gastric, hepatic and splenic arteries.

#### THE GASTRIC ARTERY

The gastric artery (*arteria gastrica sinistra*) runs upward and to the left, crosses the left crus of the diaphragm behind the peritoneum and gains the lesser curvature of the stomach near the cardiac end by arching forward between the two layers of peritoneum which are reflected from the stomach and esophagus on to the diaphragm. On reaching the stomach the artery gives off an esophageal branch which





cated, or only one, more frequently the posterior branch, will anastomose with the non-bifurcated pyloric artery (Figs. 2 and 3). In other cases there is no end-to-end anastomosis with the pyloric on the surface of the stomach; each branch is lost by the perforation of its secondary divisions into the muscular coats of the stomach; the anastomosis then takes place in the submucosa. Because of the absence

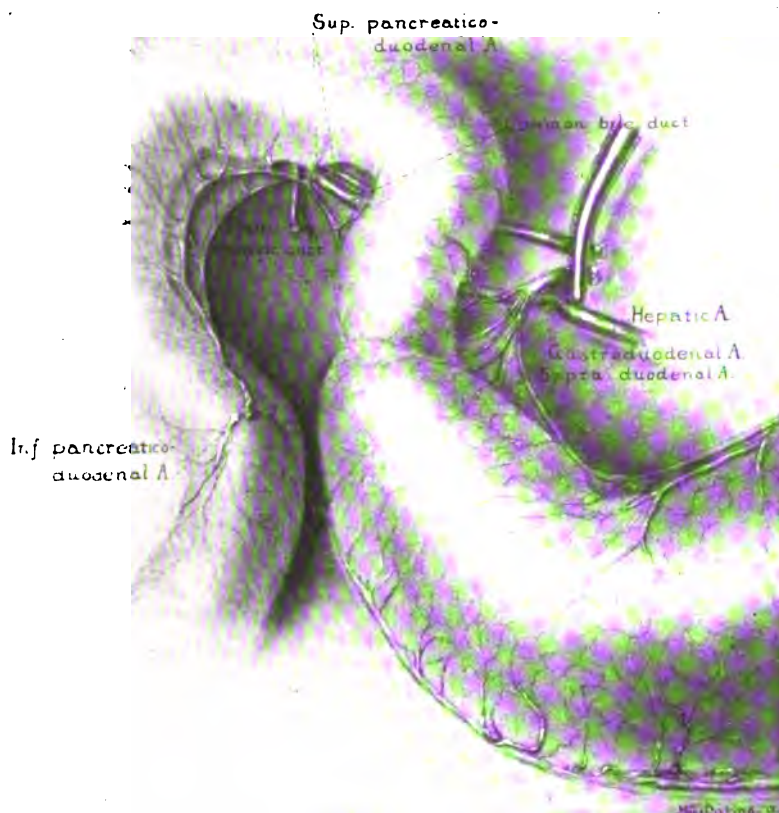


FIG. 3.—Dissection showing the blood vessels and their relations to the pyloric end of the stomach and the duodenum. Anterior view. Pancreas dissected away.

of the pyloric artery in a very few instances no sort of anastomosis can be found. Leriche and Villemin found no anastomosis in 6 of 55 cases. In a single case of my series of 62 cases no anastomosis could be found; this was due to the absence of the pyloric artery. From the arcade along the lesser curvature there are from 3 to 5 branches which run downward on both the anterior and posterior wall

for a variable distance to penetrate the muscular coats. A second group of very small arteries enters directly through the muscular coats on the lesser curvature.

### THE HEPATIC ARTERY

The hepatic artery runs slightly forward and to the right over the right crus of the diaphragm and along the upper border of the head of the pancreas behind the posterior layer of the lesser sac of peritoneum. It bends forward, crosses the left surface of the portal vein, and enters between the two layers of the gastrohepatic omentum at the upper margin of the duodenum. It then courses upward and to the right to the porta hepatis of the liver lying in the free margin of the gastrohepatic omentum in front of the portal vein and to the left side of the common bile duct. On entering between the two layers of the gastrohepatic omentum the hepatic artery gives off the pyloric artery (*arteria gastrica dextra*). This vessel descends between the two layers of peritoneum to the pylorus, giving off branches both to the anterior and posterior surfaces, which usually anastomose with the duodenal vessels in the submucosa. The artery terminates on the lesser curvature of the stomach as described. The gastroduodenal artery is given off from the hepatic soon after the pyloric. It varies from one-half to one inch in length and descends behind the first part of the duodenum about three-fourths of an inch to the right of the pylorus, where it terminates by dividing into the superior pancreaticoduodenal and the right gastro-epiploic. The right gastro-epiploic usually gives off one or two very small branches to the lower margins of the first part of the duodenum, then enters between the two layers of the gastro-colic omentum to run along the greater curvature of the stomach and anastomoses with the left gastro-epiploic from the splenic. From this arch branches are given off at much more frequent intervals than on the lesser curvature. Although arteries from the lesser curvature are fewer in number they run a longer course (Figs. 2 and 3). The branches from both arches run in the serous coat for a short distance, then perforate the muscular layers to form a very extensive series of anastomoses in the submucosa.

### THE SPLENIC ARTERY

The splenic artery (*arteria lienalis*) runs a rather tortuous course more or less horizontally to the left over the left crus of the diaphragm,

left suprarenal and upper pole of the left kidney, and just above the upper margin of the pancreas behind the posterior wall of the lesser sac of peritoneum. On leaving the region of the kidney it enters between the two layers of the lienorenal ligament and breaks up into several branches which enter the hilus of the spleen and at the same time give off the right gastro-epiploic and several short gastric branches. These vessels enter between the two layers of the gastrolial ligament and pass on to the greater curvature of the stomach. The left gastro-epiploic runs to the right and by anastomosing with the right gastro-epiploic it forms the arcade of the greater curvature. The short gastric branches are distributed to the left end of the greater curvature where they help to supply the fundus, and they pass to both anterior and posterior surfaces and anastomose in the submucosa with the cardiac branches of the left gastric and left gastro-epiploic arteries.

#### ARTERIES OF THE GASTRIC SUBMUCOSA AND MUCOSA

On examining the plexus or series of anastomoses made by the arteries in the submucosa it is found that there is quite a marked difference between those of the lesser curvature and those of the rest of the stomach. Compare Figures 5 and 6.

All the arterial branches destined to supply the stomach penetrate the muscle coats and enter the submucosa where they form a very extensive plexus, or net-work of comparatively large vessels. Those from both curvatures anastomose freely with each other and reach across to anastomose with those of the opposite curvature (Fig. 4). The plexus is remarkable in that all the vessels run a very tortuous wavy course and give off branches which are to a great extent of equal size throughout the entire stomach except along the lesser curvature. Since the submucous plexus on the lesser curvature is different from that in other parts of the stomach, I shall describe it separately: It is made up by small perforating branches from the main trunks along the lesser curvature. On entering the submucosa these vessels bifurcate and run more or less parallel with each other between the esophageal opening and the pylorus. They are much smaller, make fewer anastomoses and run more than twice the distance of the same sized vessel in any other part of the stomach (Fig. 5). By means of rather small branches this plexus anastomoses with those on the anterior and posterior walls. The two plexuses have the same relative

position in the wall of the stomach, that is, midway between the inner muscle coat and the muscularis mucosa. In an injected speci-

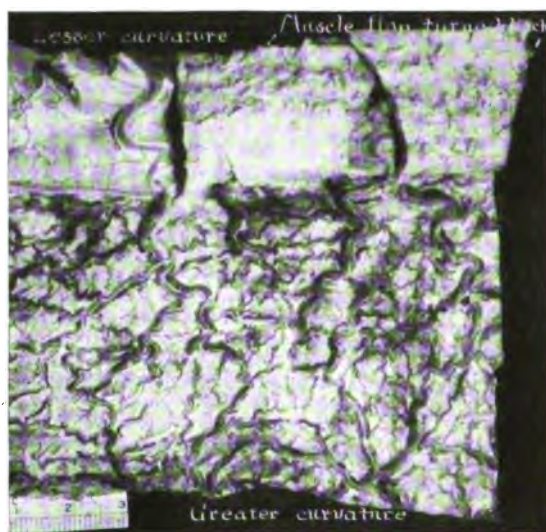


FIG. 4.—Arteries of the submucosa of the posterior wall of the stomach. Note the tortuous course of the smallest branches. Dissection photograph.

men it is quite easy to dissect away either or both the mucous and muscular coats.

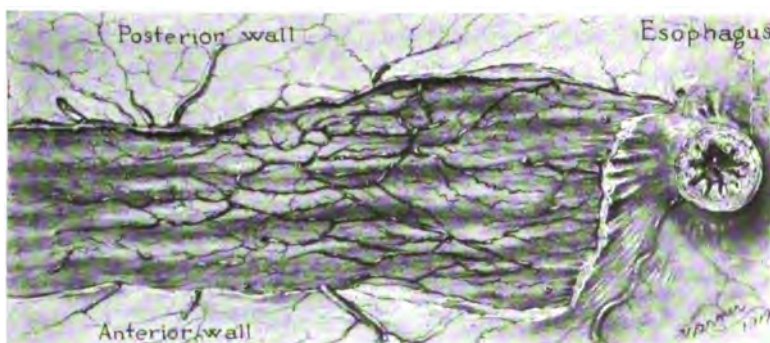


FIG. 5.—Dissection illustrating the submucous plexus of arteries on lesser curvature of stomach. Note the length, size, and general direction.

From the plexus of arteries in the submucosa two systems of branches are given off; one passes to the muscular coats and the other to the mucous coat. I shall not describe the former. In many respects



**FIG. 6.**—Arteries of stomach mucosa with a few capillaries injected. Photomicrograph ( $\times 50$ ).



**FIG. 7.**—Vessels entering the gastric mucosa. Note the sudden diminution in size of the vessels. Many branches are not injected because of plugging with carmin granules. Photomicrograph ( $\times 50$ ).

my findings agree with the investigations of Disse published in 1904. The system of vessels going to the mucosa is somewhat complicated. The vessels run in a slanting direction toward the muscularis mucosa and at the same time take a very tortuous course. They usually divide twice before reaching the muscularis, the branches having the same spiral-like course, often twisting about each other and in this manner passing through the muscularis mucosa. As they enter into the mucosa they suddenly become smaller by giving off branches that are terminal arteries, connected only by means of a capillary network (Figs. 6 and 7). These vessels continue to run a rather winding course and it seems that the transition from arterioles into capillaries may take place anywhere in the mucosa, but for the most part the change is in the deepest half. According to Disse each end-artery supplies an area of mucosa about 2.5 mm. in diameter. From the character and arrangement of the arteries in the submucosa, it would seem that they are markedly well adapted for the regulation of the blood supply to the mucosa.

#### ARTERIES OF THE DUODENUM

The duodenum, except for its first one and one-half inches, receives its blood supply entirely from the superior and inferior pancreaticoduodenal arteries. The superior is one of the terminal branches of the gastroduodenal, and arises behind the duodenum about three-fourths of an inch to the right of the pylorus. It inclines to the right and soon divides into an anterior and posterior branch. These, however, may come off separately from the gastroduodenal (Fig. 8). The two branches run downward between the duodenum and the head of the pancreas; they are both overlapped by the thin margin of the pancreas projecting in front of and behind the margin of the duodenum. The posterior of these branches runs in intimate relation with the lower portion of the common bile duct (Figs. 3 and 8). The inferior pancreaticoduodenal is given off from the superior mesenteric just before the latter passes in front of the third part of the duodenum. It runs to the right behind the superior mesenteric vein and soon divides into anterior and posterior branches which run along between the duodenum and the pancreas to anastomose with the two branches of the superior pancreaticoduodenal, thus making two arcades in the curvature of the duodenum as shown in Figures 3 and 8. From these two

arcades, branches pass quite regularly to the anterior and posterior walls of the duodenum and tend to encircle the bowel. After reaching the bowel they soon pierce the muscular coats and form a submucous plexus by a series of anastomosing arcades (Fig. 9). This plexus is made up of a series of branches given off from the larger arteries encircling the bowel. These branches anastomose with each other;

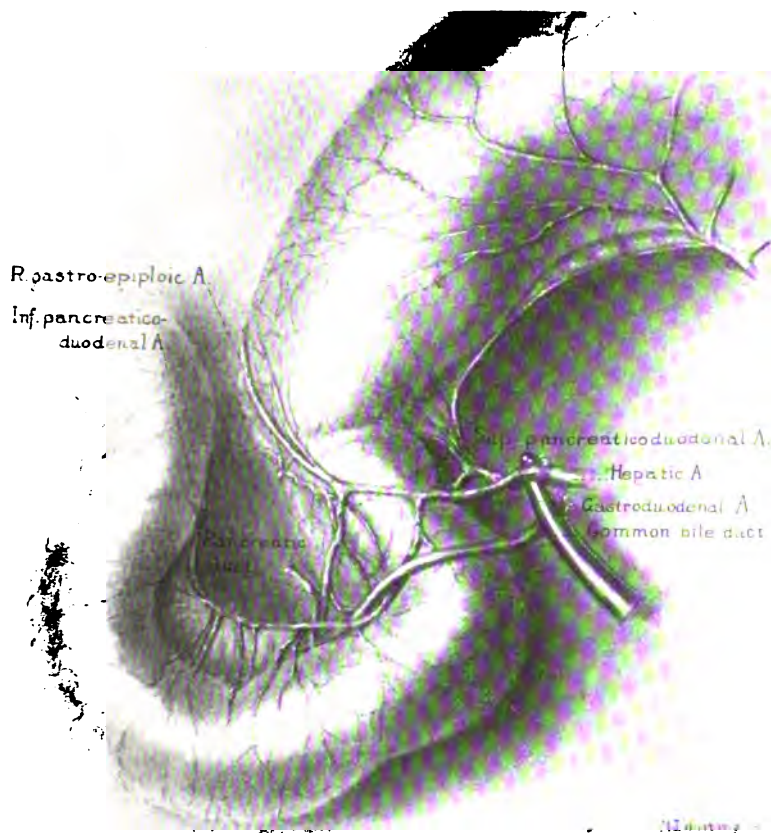


FIG. 8.—Dissection drawing showing the blood vessels and their relations to the pyloric end of the stomach and the duodenum. Posterior view. Pancreas dissected away.

they are short and relatively of the same length and caliber. The encircling vessels become gradually smaller until finally they are the same size as the anastomosing branches. Under these conditions it seems that the blood pressure must be the same in all branches entering the mucosa, thus insuring a constant blood supply to all parts of the mucosa. From the submucous plexus vessels are given



off to supply the muscular coats; these vessels will not be described here. The greater part of the blood stream is carried to the mucosa

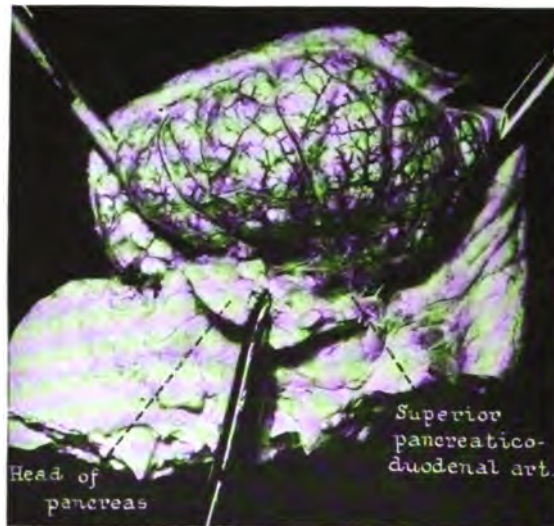


FIG. 9.—Anterior wall of the second part of the duodenum; muscular flap dissected away. Photograph of specimen.

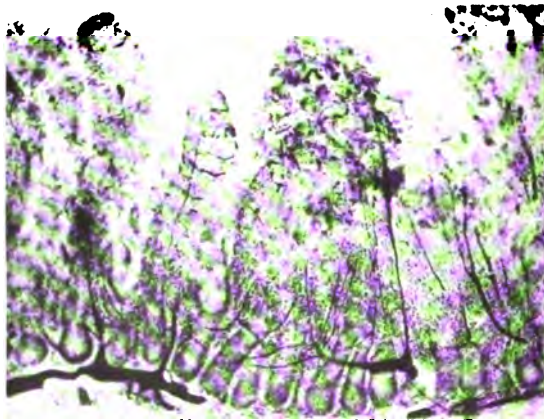


FIG. 10.—Villus and crypt type of arteries in duodenum. Capillaries injected. Photomicrograph ( $\times 50$ ).

through two sets of arteries, one to the villi, and one to the lower ends of the crypts. The arteries, on piercing the muscularis, give off a



FIG. 11.—Dissection photograph showing submucous plexus of arteries. First part of duodenum. Note how the vessels are in the first inch.



FIG. 12.—Gastric type of spiral artery in the duodenum. Branches plugged with carmin granules, hence no other vessels in the field. This is in itself suggestive of a terminal artery. Photomicrograph ( $\times 100$ ).

variable number of branches to the villi, there being usually one to each villus. This artery passes almost through the center and terminates in capillaries near the summit (Fig. 10). The crypt type of artery, on entering the mucosa, divides into several branches which radiate in all directions, and run along the bases of the glands (Mall). These in turn give off branches which pass upward around the glands and soon terminate in capillaries which supply the glands and stroma (Fig. 10).



FIG. 13.—Gastric type of spiral artery entering mucosa of duodenum. Branches plugged with carmin gelatin. Photomicrograph ( $\times 100$ ).

The first one and one-half inches of the duodenum receive their blood supply chiefly from an artery which is usually given off from the gastroduodenal or hepatic. This vessel has been described at length by Wilkie under the name of "supraduodenal artery." From its origin, as shown in Figures 2, 3, and 11, it runs downward between the two layers of the lesser omentum to the upper margin of the duodenum. Here it gives off a small branch to the posterior surface of the duodenum while the main vessel comes on the anterior surface to anastomose rather sparingly with a small branch of the pyloric, a small branch of the right gastro-epiploic, and with branches of the superior pancreaticoduodenal (Fig. 11). The posterior wall of the first one and one-half inches of the duodenum is supplied chiefly by small branches from the gastroduodenal artery, given off as that vessel

passes behind the bowel. It also receives some small twigs from the supraduodenal, pyloric, and right gastro-epiploic arteries. These arteries, soon after reaching the wall of the duodenum, penetrate the muscular coat and form a submucous plexus which is strikingly different from that lower down in the bowel. Compare the first and second halves of Figure 11. The first inch certainly has very few arteries in the submucosa in comparison with other parts of the duodenum. It would seem that this explains the observation of

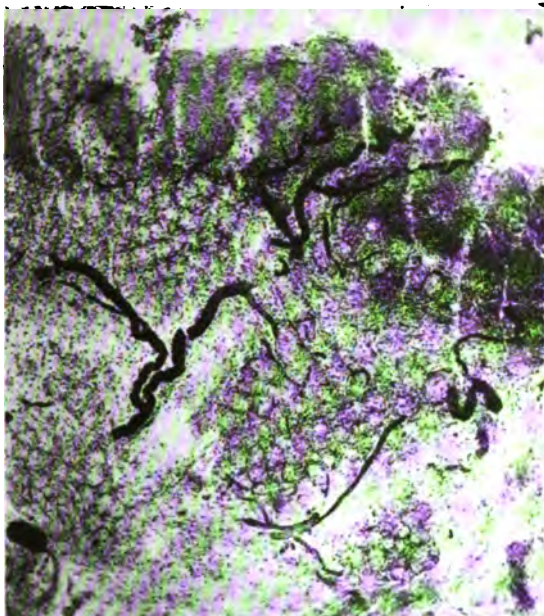


FIG. 14.—Gastric type of artery in first inch of the duodenum, giving off villus branches. The smaller cryptic branches are plugged with injecting material. Photomicrograph ( $\times 50$ ).

W. J. Mayo regarding the "anemic spot" produced by traction, usually seen on the surface of the bowel in this region. From the submucous plexus of vessels branches are given off to the mucosa which simulate to a marked degree the vessels of the stomach. They are not quite so large nor do they run so consistently tortuous a course. Yet many are definitely of the spiral gastric type; this is particularly noticeable just as they enter the muscularis mucosa (Figs. 12 and 13). Beside the gastric type of crypt vessels in the first inch of the duodenum is the villus type; and since the villi are not so numerous

nor so high as they are farther down in the bowel, these arteries are correspondingly modified (Fig. 14). There are possibly a few more arteries in the submucous plexus on the posterior than on the anterior wall of this portion of the duodenum otherwise the blood vessels are similar.

The transition from stomach to duodenum is not sharply marked either in the mucosa or in the submucosa. Brunner's glands are often found in the pylorus and the pyloric glands frequently extend over into the duodenum (Bailey). In fact, Brunner's glands are believed by Oppel and others to be a continuation of the pyloric glands. Certainly the gastric type of artery is carried over into the duodenum, the change being gradual. According to Mall, the crypt vessels of the small intestine become submucous vessels in the stomach and the arteries to the villi become smaller and are the stellate vessels of the mucosa in the stomach.

#### THE SIGNIFICANCE OF GASTRIC AND DUODENAL ARTERIES IN RELATION TO ULCER

The character of the arteries of the submucosa and of the mucosa of the stomach from a normal as well as from a pathologic standpoint has a physiologic significance. The glands secrete chiefly during digestion when the walls of the stomach are expanded; during this period they need a rich blood supply. From a physiologic standpoint it is of advantage to the organism if the flow of blood to the capillaries of the mucosa is made less difficult when the stomach is filled, and that the blood supply is limited when the stomach is empty. With a full stomach, when the walls are expanded, all of the rugæ or folds of the mucosa disappear except two along the lesser curvature; all the winding spiral curves and marked tortuosities of the arteries are straightened out, except those along the lesser curvature; thus the resistance offered the blood stream by the very tortuous arteries decreases and the flow of blood to the mucosa is made less difficult (Waldeyer). Of course, there is undoubtedly a nervous influence at work at the same time, causing a dilatation of the vessels. But the latter influence is entirely separate and distinct from the mechanical resistance offered by the vessels. As the stomach empties itself and becomes gradually smaller following digestion, the arteries of the mucosa and submucosa become more tortuous and the blood meets with greater resistance.

Thus the blood content of the mucosa is not nearly so great in an empty as in a full stomach.

Among the most generally accepted theories advanced regarding the etiology of gastric and duodenal ulcer is the theory that they are caused by a hematogenous infection. The clinician and the surgeon in their attempts to establish a cure for ulcer are realizing more and more that they are dealing with an infectious process.

Pathologic changes in the vessels result in marked changes in the blood flow, due not only to partial obstruction, but also to a diminished elasticity and contractility of the arterial walls. Virchow was among the first to call attention to the fact that thrombosis or other vascular lesions producing obstruction of the vessels in the gastric mucosa result in hemorrhagic necrosis which, in the presence of the gastric juice, leads to ulcer. A local end-arteritis producing practically an obstruction of a vessel, which makes few or no anastomoses and supplies relatively a large area of the mucosa, probably causes a chronic gastric ulcer in rare instances in elderly persons, just as superficial ulcers and even gangrene are produced elsewhere by the same cause. This type of ulcer will not heal, probably because of the lack in power of the diseased vessels to regenerate new ones to supply the affected area with arterial blood. Various observers in their attempts to produce gastric and duodenal ulcer by disturbing the circulation have shown that embolism of the vessels entering through the muscularis mucosa gives the most pronounced results. The collateral circulation of the vessels in the submucosa is so great that one of the four large vessels passing on to the wall of the stomach may be ligated without causing harm to the stomach (Baumann). The collateral circulation in the mucosa, however, is limited, for the most part, to capillaries.

Cohnheim, in 1890, produced acute ulcers by the injection of foreign substances into the gastric circulation. In these cases the injecting material seemed to occlude the vessels entering the muscularis mucosa and to cut off the circulation to a limited area of the mucosa. The action of the gastric juice on the dead or devitalized tissue probably contributed to the production of acute ulcers. This type of ulcer heals readily since there is nothing to cause additional destruction of tissue, and since the natural tendency of the body is to repair the damage done.

Rosenow injected streptococci isolated from gastric and duodenal ulcers in man into the venous circulation of experimental animals and

produced gastric and duodenal ulcer in 60 per cent, and a total of ulcer and hemorrhage in 83 per cent of the animals injected. I quote from his summary: "The ulcers produced by the injection of streptococci resemble those in man in location, in gross and microscopic appearance, and in that they tend to become chronic, to perforate, and to cause severe or fatal hemorrhage." According to Rosenow's description, "both the circumscribed hemorrhage and the ulcer are cone-shaped with the base of the cone at the surface and the apex at the muscularis." From the anatomic arrangement of the vessels in the mucosa, this circumscribed area of hemorrhage is just what one would expect from thrombosis or disturbance of the circulation of the vessels entering through the muscularis mucosa. Since this type of ulcer is produced by streptococci it tends to become chronic and to have all the characteristics of ulcer in man; the streptococci serve as a constant irritant and prevent healing. The continued action of the localized infection in the deep layers produces local circulatory disturbance, hemorrhage, anemia and so forth. Since the gastric juice digests devitalized tissue, and since the vascularization of the underlying tissue may become gradually less, perforation may be the final outcome.

As has been stated, the rugæ of the stomach mucosa disappear with expansion of the walls. There are two folds, however, one anterior and one posterior, along the lesser curvature extending from the esophageal orifice toward the pylorus which do not disappear (Waldeyer). Lewis has shown these folds on his reconstruction models of the stomach in the human fetus. He has described a canal along the lesser curvature which he named "canalis gastricus." Waldeyer in his review of this subject states that these folds become larger with the filling of the stomach and finally form a canal running lengthwise of the lesser curvature. When a stomach is distended with air or fluid even to the point of rupture the lesser curvature takes comparatively little part in the distention and the break always occurs at the fundus. I have noticed particularly that it is more difficult to get a good injection of the vessels in the mucosa of the lesser curvature than elsewhere, even with distention of the stomach. This is also true of the first inch of the duodenum. Mall, in his work on dogs' stomachs, reports similar difficulties in injecting the vessels of the pylorus and of the beginning of the duodenum.

The vessels of the mucosa on the lesser curvature are not essentially

different from those in the rest of the gastric mucosa. But the arteries making up the submucous plexus are very much smaller and make longer anastomoses than those in the rest of the submucosa. Due to the permanent folds the vessels along the lesser curvature do not have so great an opportunity to straighten out with moderate distention as those in other parts of the stomach. Thus the resistance offered the blood stream by the much smaller and constantly winding tortuous arteries is never removed. As a result the blood current entering the mucosa is constantly slower and at a lower pressure than in any other region of the stomach. Hence it seems the arteries are more liable to thrombosis.

As I have stated, the arteries making up the submucous plexus in the first inch of the duodenum are comparatively few in number. They are rather small and do not anastomose freely. From this plexus we find along with others the gastric type of spiral tortuous artery entering the mucosa. The mucous lining is practically devoid of folds; distention therefore has little effect toward the straightening out of these vessels. The rather limited blood supply in itself to this area of the duodenum probably causes a slower blood current. Further, the presence of gastric type of artery offers a remarkable resistance to the blood stream. Due to these conditions it seems that the arteries of the first inch of the duodenum are more liable to thrombosis than those of any other region.

#### CONCLUSIONS

This investigation shows that the anatomic arrangements of the arteries along the lesser curvature of the stomach and throughout the first inch of the duodenum are such that the arteries are predisposed to thrombosis. The plexus of vessels in the submucosa on the lesser curvature is made up of much smaller and longer arteries without as free anastomoses as in other regions of the stomach. The branches from this plexus run a very tortuous course to enter the mucosa. The resistance offered the blood stream is constantly greater and, as a result, the blood current is slower as it enters the small arteries of the mucosa. The submucous plexus of arteries in the first inch of the duodenum is made up of relatively few vessels in comparison with other parts of the duodenum. They are small and do not anastomose freely; they give off branches to the mucosa some of which simulate the gastric type of spiral artery. The rather limited blood supply



and the gastric type of artery predispose to thrombosis. Since the vessels are more liable to be occluded by emboli, it is reasonable to suppose that they are an important factor in the production of ulcer by hematogenous infections.

By these observations I wish to call attention to the character and distribution of the smaller arteries in stomachs and duodenum altogether anatomically normal, and to submit the hypothesis that possibly slight deviation from the normal may contribute to peptic ulcer. In any consideration of ulcer it must be remembered that this disorder is relatively and actually rare; according to Osler ulcer is found at 1.32 per cent of all necropsies performed in the United States and in Canada. Finally, it must be remembered that high grade bacteremias do not frequently produce gastric or duodenal ulcer.

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## ANGIOMA OF THE STOMACH\*

W. S. LEMON

In this report, I wish to add one more case of angioma of the stomach to the five of which I have knowledge, namely, the cases reported by Guisez, Stockis, Burty, Lammers, and, recently, one by Sherril and Graves. The clinical aspect of the case came under my observation; it was studied pathologically by Dr. Broders, who examined the specimen at the time of operation.



FIG. 15 (Case A258233).—Photograph of hemangioma of the stomach as it presented on the mucous surface.

*Macroscopic examination.*—The tumor was irregular in shape, bluish-black, rather soft, having the feel of a mass of angle worms, and measured 6 by 5 by 5 cm. It was surrounded by a fibrous capsule ranging from 1 to 2 mm. in thickness. Bands of fibrous tissue between the dark angiomatous areas made it appear not unlike an anthracotic lung. The tumor lay between the mucosa and serosa,

\* Reprinted from Med. Rec., 1920, xcvi, 220-222.

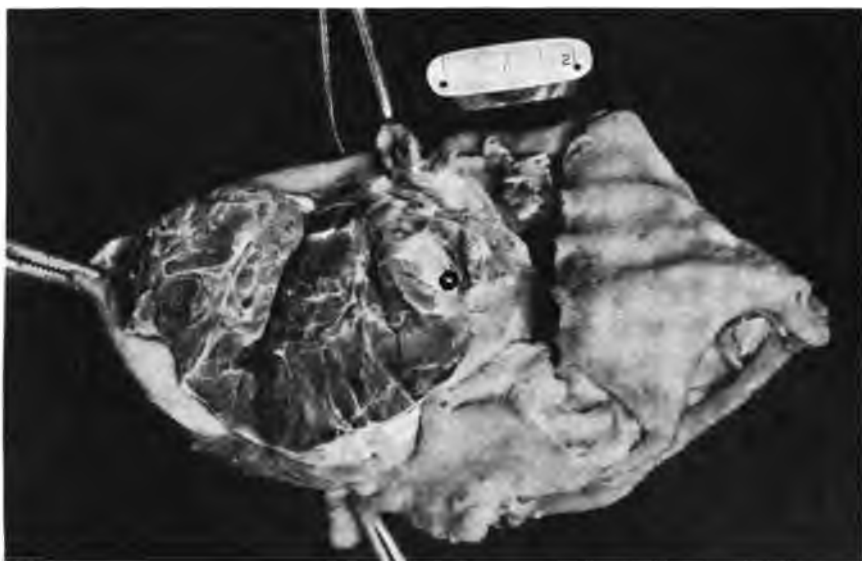


FIG. 16 (Case A258233).—Photograph of hemangioma of the stomach after section. Note its marked lung-like appearance.

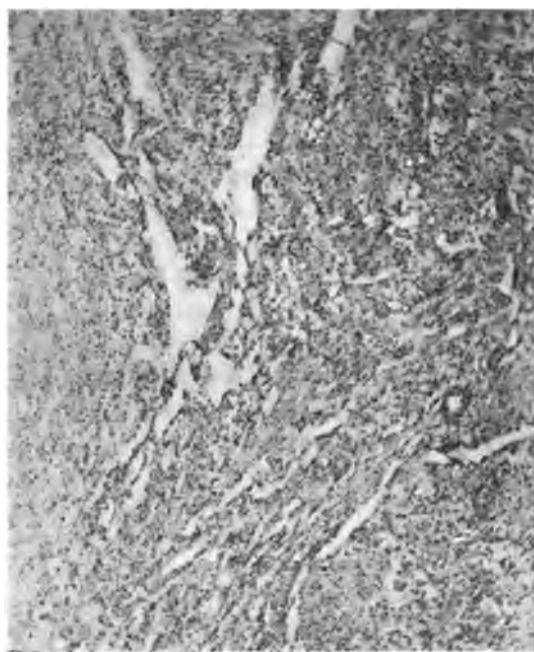


FIG. 17 (Case A258233).—Photomicrograph of hemangioma of the stomach, showing a network of capillaries ( $\times 50$ ).

and in places it had broken through its capsule and penetrated the surrounding structures (Figs. 15 and 16).

*Microscopic examination.*—The mass was made up of a network of capillaries, some showing a fairly marked dilatation. Blood pigment could be seen both within and without the capillaries. Some fields were entirely of angiomatous tissue, while others showed muscle with small groups of capillaries. A few clusters of lymphocytes were found in some of the fields. A diagnosis of capillary hemangioma was made (Figs. 17 and 18).

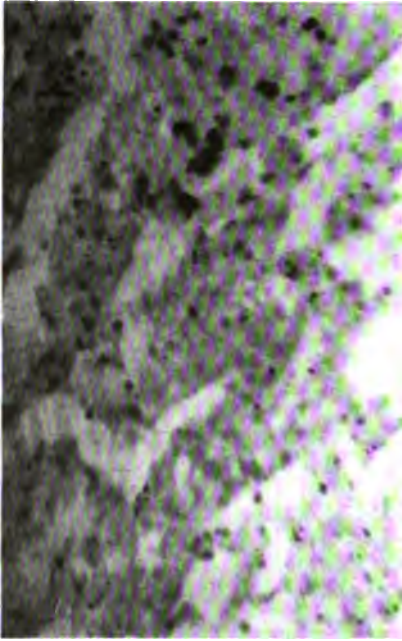


FIG. 18 (Case A258233).—Photomicrograph of hemangioma of the stomach, showing patches of blood pigment in the capillaries ( $\times 50$ ).

#### HISTORY OF THE PATIENT

Case A258233. Jan. 28, 1919, a man, aged 67, presented himself for examination, complaining of distress in the epigastric region. The patient was large, fully 6 feet tall, and weighed 202 pounds, although he showed but slight evidence of adiposity. His habits of life were exemplary and his trouble could not be traced to any indiscretion or excess. The previous history was unimportant. Six years before he had had two minor operations, the correction of a varicocele,

and the removal of an epithelioma of the lip. After the removal of the epithelioma he had been treated for several months by the x-ray; there had been no evidence of recurrence.

His gastric trouble had extended over a period of about six months; it had been initiated by an exhausting, but not painful, diarrhea. The stool was "tarry" and contained much blood. Following this attack and two months before his present examination, he had felt an indefinite aching pain located at the left costal arch and sufficiently urgent and persistent to cause wakefulness and to make work almost impossible. The pain had taken on a diffuse character and radiated downward and inward toward the lower quadrants.

Dietetic treatment had been advised, milk being used as a basis, but this increased rather than lessened the distress. A barium meal, taken when an x-ray plate was made, proved to give him great comfort. This meal was repeated at the end of a week. The x-ray plates of the stomach showed a large unfilled area in the fundus and the splenic flexure of the colon seemed fixed out of its normal position. The descending aorta was considerably dilated and was thought to have been so for many years, as a cough during that time had suggested pressure on the recurrent laryngeal nerve.

Two weeks before examination, the patient had been conscious of some indefinite pain, located at the right costal margin, but his appetite had been good, and food taken relieved rather than distressed, although a certain sense of fullness with discomfort was commencing. He had had, however, no vomiting and no hemorrhage by mouth and there had never been urgent colic nor jaundice. He had lost 25 pounds in weight, was dyspneic on exertion and easily fatigued, and had had a slight cyanosis.

Physical examination revealed a loose skin, muscles somewhat atonic, and a loose and pendulant abdomen, adiposity 2 on a scale of 4, cyanosis 1, a well marked arcus senilis, and arteriosclerosis 3. The systolic blood pressure was from 220 to 240; the diastolic pressure remained constant at 120. The urine was normal with the exception of albumin 2, and hyaline casts 1. The pulse was 72 and regular. Examination of the mouth, nose, and throat revealed oral sepsis and several carious teeth. Increased areas of dullness beneath the sternum and marked left ventricular hypertrophy were found, although the heart sounds were clear, without irregularity, and the heart itself was compensating satisfactorily. The lungs were clear, the liver was not

enlarged, and there was no evidence of edema in the extremities. The epigastric area was carefully examined by several consultants; there was no evidence of palpable tumor or other abnormality. The highest readings made during the fractional examination of gastric contents gave a total acidity of 50 per cent and a free acidity of 30 per cent.



FIG. 19 (Case A258233).—X-ray of chest showing dilated aorta.

The roentgenographic studies were interesting in that they confirmed previous examinations, namely, an aneurysmal dilatation of the aorta (Fig. 19), the thoracic aorta taking on the appearance of a conical sac-like body, and a filling defect in the body of the stomach which the roentgenologist believed to be caused by a cancerous growth, the operability of which was questionable because of its location (Fig. 20). The one difference in the x-ray examination made at this clinic from that made elsewhere was the finding of what ap-

peared to be a normal colon, the displacement of the splenic flexure not being confirmed.

The roentgenologist's diagnosis of cancer of the stomach was confirmed clinically, but in view of its location, the marked hypertension, and the advanced age of the patient, surgical intervention was not advised. The patient, a surgeon himself, realizing that an explora-



FIG. 20 (Case A258233).—X-ray of stomach showing filling defect.

tion promised him little, at first chose not to have an operation. After several days' consideration, however, he determined to take what little chance of improvement there might be.

At operation February 5, (W. J. Mayo) a tumor 6 by 5 by 5 cm., which pathologic examination proved to be an angioma, was found lying in the fundus of the stomach; it was quite freely movable and presented easily. About 11 cm. of the center of the stomach were removed, a sleeve resection and an end-to-end anastomosis made.

The convalescence was uneventful; the patient returned to his home on the second of March, twenty-five days after operation, with the wound healed. Two months later he reported that so far as the operation was concerned, everything had been "eminently satisfactory." He had a very good appetite and was able to eat almost everything and his early distress from sour fermenting stomach had improved materially. Six months after operation he was enjoying good health and was engaged in his medical practice.

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## THE OPERABILITY OF CANCER OF THE STOMACH AS DETERMINED BY THE X-RAY\*

R. D. CARMAN

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An important diagnostic aid which can give much preoperative information with regard to operability of lesions of the stomach is the x-ray. It can demonstrate the size, the shape, and the position of the stomach, important factors with which the surgeon has to reckon, as well as the size, the location, and the extent of the lesion. It can show whether a stomach suspected of disease is normal, whether a tumor is present, and whether the tumor is intrinsic or extrinsic. The roentgenologist, by basing his judgment on the sum of knowledge gained from the x-ray, can point out whether a cancer or lesion of the stomach is operable or not, insofar as the stomach is concerned; but it remains for the internist and the surgeon to advise operation, and for the surgeon to decide on the kind of operation. The earlier the lesion is discovered, the less will be their quandary.

Without the use of the x-ray, a diagnosis of cancer of the stomach is often not made until cachexia, loss of weight, achlorhydria, obstruction, Oppler-Boas bacilli, and a palpable tumor are noted; these are all signs of advanced gastric cancer. The patient's fate depends too much on his physician's personal opinion and too little on the true but hidden conditions of the case. As many physicians have believed, and still believe, that the presence of a palpable tumor precludes operative relief, some patients whose lives might be prolonged by operation are not operated on. Others are subjected to useless exploratory laparotomies which x-ray examination can prevent.

The roentgenologist does not look on this method of examination as independent or ultimate, as it is only one part of a thorough clinical examination, and the verdict of operability based on its findings is only of relative value except in cases that are indisputably inoperable. The syndrome of early cases of cancer of the stomach is not sufficiently

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characteristic to differentiate it from that of other gastric diseases, nor can a cellular diagnosis be made by the x-ray, but a filling defect may be shown which enables the roentgenologist to make a gross pathologic diagnosis in the majority of cases. An indication for operation should be recognized in the location and extent of the filling defect in the gastric contour, especially when we consider that 95 per cent of all tumors of the stomach are cancerous. As metastasis and an extended lesion prevent operation in many more cases than does the location of the primary lesion, early diagnosis seems the surest preventive of a high gastric cancer mortality; the x-ray has often proved to be a means of diagnosis and of forecasting the operability of carcinoma of the stomach at a time when clinical symptoms are so slight as merely to hint at malignancy.

The eliminative value of the x-ray in gastric diagnosis applies to the healthy as well as to the diseased stomach. An x-ray examination of patients who complain of such symptoms as indigestion and dyspepsia, conditions which are often manifestations of other gastric and extragastric disorders, may result in negative findings. The outline, size, shape, and position of the stomach prove that the stomach is normal and only the victim of reflex disturbances which the x-ray may aid in finding. If the x-ray examination reveals a tumor of the stomach, however, screen and plate findings should be studied with one purpose in mind—possible cure by operation. The chances for cure which the particular case possesses place it, according to the x-ray evidence of operability, in one of three groups: operable, borderline, or inoperable. The limits of each group are roughly marked by the roentgen divisions of the stomach: Group 1, tumors of the pars pylorica, the operable zone; Group 2, tumors of the pars media, the questionable or borderline zone, and Group 3, tumors of the pars cardiaca, the definitely inoperable zone.

### OPERABLE TUMORS

In Group 1 are those tumors which are located in the pyloric end of the stomach; these are shown by the x-ray to be operable "insofar as the stomach is concerned." In this type are included those cases in which the lesion has not spread far on the stomach wall to the danger zone, the pars media (Fig. 21). As approximately 70 per cent of all gastric cancers occur in the pyloric end of the stomach,

and as about 95 per cent of all lesions which encroach on the gastric lumen are carcinomatous, a lesion in the pyloric end should always make one strongly suspicious of malignancy. The character and size of the filling defect may also give some hint, but the question of malignancy which is of importance in considering the advisability of operation is of no importance from the standpoint of the possi-



FIG. 21 (263349).—Filling defect and obstruction due to tumor of the pyloric end of the stomach. The irregularity corresponds to a palpable mass. The lesion is operable "so far as the stomach is concerned."

bility of operation; that depends on the amount of healthy stomach wall remaining. Often cases which present such severe symptoms clinically as to seem inoperable prove operable on x-ray examination, for even a very large palpable tumor may be resected if it is confined to the lower half of the stomach. While a palpable tumor does not, therefore, prevent surgical intervention, it does mean that the lesion has existed for some time and that metastasis may be present. Free

motility of the cancerous stomach favors resectability, but the signs which point to it may also be misleading. The filling defect may be atypical of cancer and the clinical symptoms alone may offer little explanation; but if the patient who has indefinite gastric symptoms has any filling defect in the contour of the stomach, whether typical or atypical of cancer, the chances are that a malignant growth is present (Fig. 22).

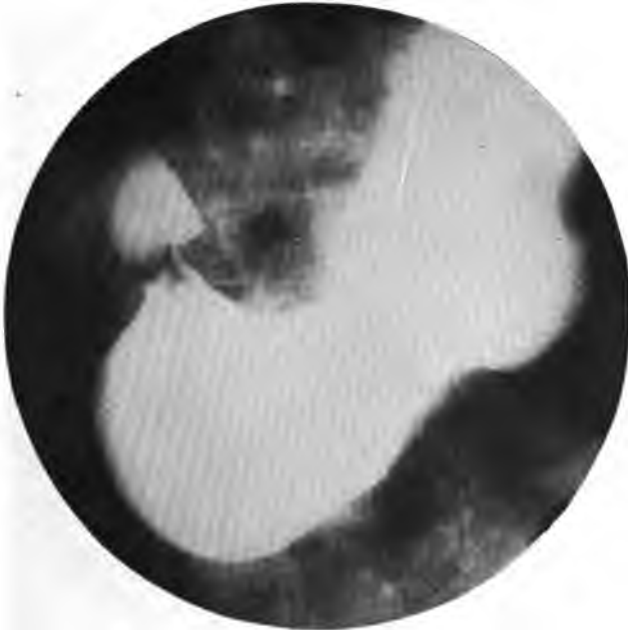


FIG. 22<sub>1</sub> (134942).—A small filling defect immediately prepyloric, with obstruction. No corresponding palpable mass. Lesion favorable for operation.

According to Deaver, the importance of the x-ray rests on the demonstration of a surgical condition in the stomach, not on the power of differentiating the condition. It is true that it cannot in 100 per cent of the cases distinguished between cancer and ulcer, and in the doubtful cases all other methods of differentiation must yield to exploratory incision and pathologic examination. This exploratory method of diagnosis was advocated by W. J. Mayo twenty-one years ago. We know now, however, that the x-ray can detect the primary lesion in a very early stage, and if, as Deaver has stated in a recent article, almost half of the gastric cancers seem to have followed on ulcers, a lesion of the stomach cannot be too early discovered and looked on as

potentially malignant. When the x-ray examination shows a tumor in the pyloric third, the most accessible portion of the stomach, it is considered operable.

A lesion of the stomach can be pronounced operable, however, only with respect to the stomach, as perforation and metastasis almost invariably remain undiscovered until after incision. The clinician can prevent useless operations in some cases which are indicated as operable by the x-ray, as he can find metastasis to the rectal shelf,

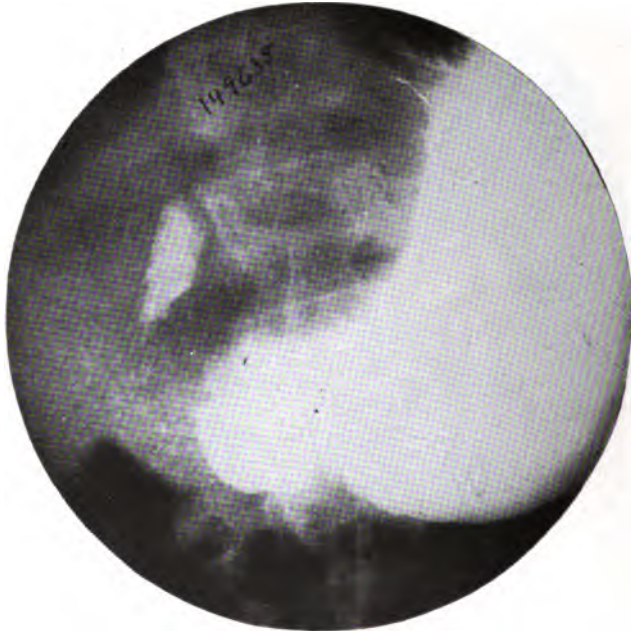


FIG. 23 (149635).—Filling defect with obstruction in the operable zone. The lesion was operable so far as the stomach was concerned, but proved to be inoperable because of metastasis found at operation.

supraclavicular glands, umbilicus, and the skin; ascites when associated with a history of malignancy is a fairly reliable index of inoperability. Gross metastasis to the lungs and bones is roentgenologically demonstrable, but it is so rare in cases of cancer of the stomach as to merit no more than mention in this brief discussion. Abdominal metastasis, the most frequent form, is a condition which neither the x-ray nor any other method of preoperative examination can discover and which the surgeon is unable to cope with, even when the tumor is in the most favorable location for resection (Fig. 23).

## BORDERLINE TUMORS

The tumors of the second group are those which extend so far up on the stomach wall, into the questionable zone, that their resection becomes uncertain; they are classed as the border-line cases. These cases present the most puzzling problems of operability from a roentgenologic standpoint. Their removal depends, as in the cases of Group 1, on the possibility of metastasis, plus the judgment and skill of the surgeon. The position and size of the stomach



FIG. 24 (106837).—Gross filling defect extending into the questionable zone. Operability of tumors of this extent can be determined accurately only by an exploratory incision. The tumor was found to be inoperable because of posterior attachment.

may be a surgical drawback; the small high-lying stomach of the robust person offers much greater difficulty to the operator than does the relaxed stomach of the asthenic person. Therefore, if the roentgenologist is familiar with the surgeon's technic he can better form his decision as to the operability of the particular case than if he knows nothing of the operator's dexterity and willingness to attempt resection when the tumor lies in the borderline zone of the stomach. The nearer the lesion approaches the cardiac zone, the more adept must be

the surgeon in order to work high up under the costal arch and to remove just enough of the stomach so as to leave it free from neoplasia (Fig. 24).

Tumors of the fundus which do not produce pyloric nor cardiac obstruction, and which are not palpable because of their high location, may exist for some time without causing much inconvenience; by the time clinical diagnosis is definite, they are usually inoperable. Also, when a tumor is in a questionable position with regard to operability, allowance must be made for the type of tumor and consequent

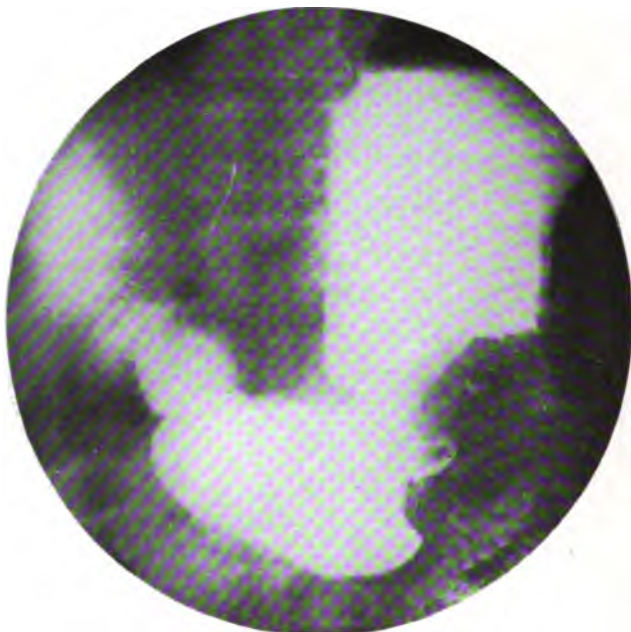


FIG. 25 (123017).—Filling defect of greater curvature involving the operable and questionable zones. Operability questionable so far as the stomach is concerned. Operation: sleeve-resection.

type of invasion of the stomach wall. The fungoid carcinomas produce multiple irregular filling defects, and the real extent of the cancer is quite closely simulated by the roentgen shadow, while the scirrhous cancer produces a filling defect less gross which may gradually shade off and not picture the true limits of the disease. Even after allowing for an excess of involvement of a scirrhous cancer, beyond that indicated, exploration may reveal inoperable conditions (Fig. 25). As free mobility of a cancerous stomach favors resectability, as fixation

resulting from extension to adjacent organs makes successful intervention less probable, as cancer roentgenologically demonstrated as small may at operation be found to have invaded or become adherent to adjacent abdominal organs, and as metastasis may exist without detection by the x-ray, the roentgenologist is forced to make such a relative diagnosis of operability in the borderline group of cases that it might be called the exploratory group, for on the surgeon devolves the operative decision.

### INOPERABLE TUMORS

In Group 3 are the cases of gastric tumors which are pointed out with finality by the x-ray as inoperable. The tumors of this group are

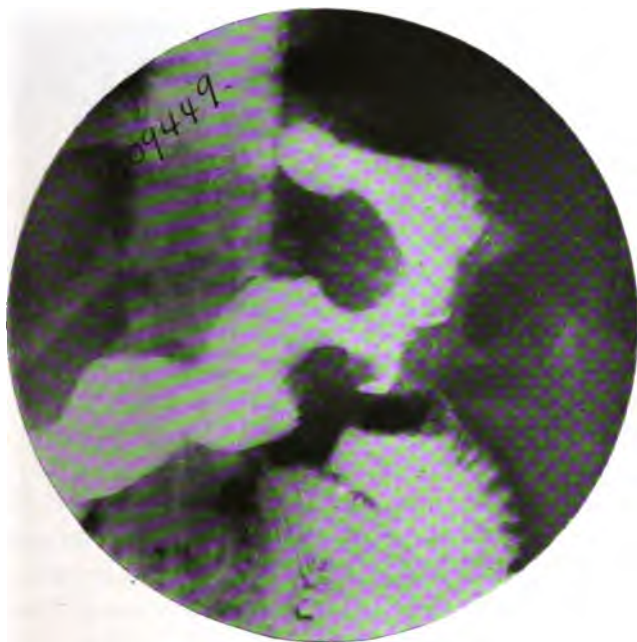


FIG. 26 (109449).—Tumor involving questionable and inoperable zones. A tumor in this location is indisputably inoperable.

located in the cardiac end of the stomach, or they have spread from a pyloric or fundal carcinoma to within this inoperable zone. Surgery can bring no relief to the patient when the cardiac end of the stomach is cancerous. The tumors in this region of the stomach are easily recognized as inoperable by the x-ray (Figs. 26 and 27).



Statistics of cancer of the stomach show an appalling number of inoperable cases, especially when it is considered that surgery may bring cure early in the course of the disease. The high fatality rate of cancer of the stomach may be largely attributed to too-late diagnosis.

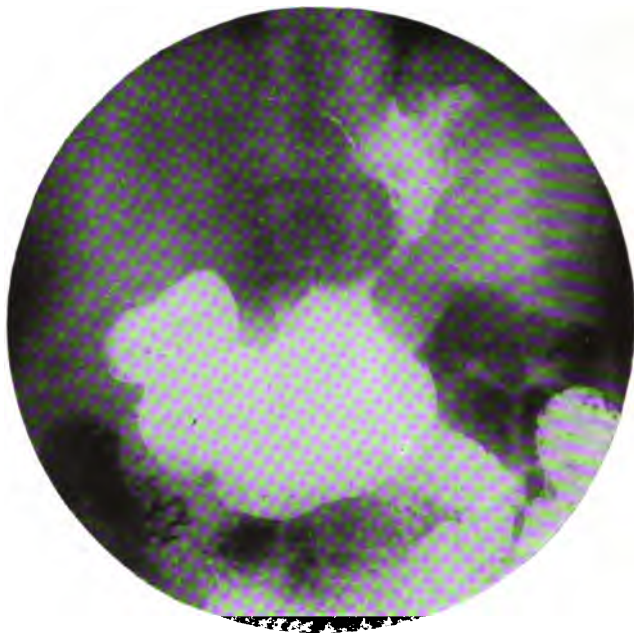


FIG. 27.—Tumor located in the inoperable zone. Operation is contraindicated in cases of this type.

### THE VALUE OF THE X-RAY

Of recent methods which have so far been adapted to discover the cancerous growth and to prophesy the chances for its removal, the x-ray signs when correlated with clinical findings seem to be the most promising means by which operability may be increased through earlier diagnosis. So many seemingly benign lesions of the stomach prove to be malignant, that the advisability of medical treatment instead of operation seems very questionable or even homicidal. Periodic x-ray examinations in a suspected case can, of course, be made, but if instead of retrograde changes a filling defect typical of carcinoma is noted in time, attempted operation may be too late because of metastasis; the watchful waiting policy often proves not to have averted operation and perhaps to have been the only cause of the patient's

early death from a malignant gastric tumor. Even though a growth may be very extensive, if it has not invaded the cardiac end of the stomach the patient should be given the chance of its successful removal through exploratory laparotomy, as some cancers evidently metastasize later than others. The exploratory incision is of little danger and it may be the means of finding a growth which has not quite reached the dividing line between operability and inoperability, that is, when the dividing line represents metastasis.

When the testimony in favor of the x-ray is collected, we find, then, that its only decisive value in predicting the operability of carcinoma of the stomach is its prevention of operation in inoperable cases. Its value in the borderline cases is limited to preoperative information with regard to the location and extent of the growth, and their significance for malignancy. In the first group, which includes the highest percentage of operable cases, the x-ray diagnosis of operable insofar as the stomach is concerned can be almost 100 per cent diagnostically correct while operability determined by metastatic conditions dwindles to about 50 per cent. As the likelihood of metastasis and the spread of the disease seem to increase with the age of the disease, it is an obvious corollary that many more patients could be successfully operated on if a diagnosis were made early.

Until all medical men and laymen realize the necessity of early examinations of all persons with any gastric complaint the death rate from gastric cancer will remain high while the successful operability rate of carcinoma remains discouragingly low. Propaganda which will direct the public's attention to the dangers of disregarding gastric symptoms seems as justifiable and perhaps as necessary as the campaigns which have decreased the death rate of tuberculosis. In 1900 the mortality statistics for all forms of tuberculosis were 201.9 for 100,000 population; in 1916 they had dropped to 141.6, more than 60 per cent.<sup>3</sup> The death rate from cancer, of which gastric cancer is the most common form, rose in that time from 63 to 81.8 for 100,000 population, more than 18 per cent. These statistics have only a relative value of course, but they do surely mean that the death rate from tuberculosis is lower than it was eight years ago, while the death rate from cancer is no lower despite the advance in surgical technic. Publicity through national and state public health departments which will lead persons who are suffering from chronic indigestion or dyspepsia, which are not diseases but only symptoms, to consult a physician, who will

conduct a thorough examination, should be one of the means of raising the operability of cancer. In every such routine examination, no matter how slight the symptoms, an x-ray examination should be included. The x-ray can now discover 95 per cent of all gastric tumors, of which only about 50 per cent are still in the operable stage. When routine examinations of persons presenting gastric symptoms become a reality, the x-ray should be able to increase the number of operative cases, for the inoperable tumors should be practically only those which cannot be resected because of cardiac location, and carcinomas of the cardia represent a small per cent of gastric cancers.

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# CANCER OF THE STOMACH AND ITS SURGICAL TREATMENT\*

C. H. MAYO

Probably no word in medicine is more depressing to the patient than that of cancer in the diagnosis of his disease. We are assured by most clinicians that cancer is on the increase; possibly this increase is more apparent than real and is due to the greater general diagnostic ability of the medical profession and the better facilities for obtaining statistics. A general knowledge, as well as fear, of the disease is gradually spreading, largely the result of the propaganda of the publicity committee of the American Medical Association, and the work of the special cancer commissions, all of which are creating a favorable evolution of opinion, and causing more persons to seek treatment during the earlier stages of the disease.

The most common cancer is that of the stomach. More than one-third of the cancers in men and more than one-fifth of the cancers in women appear in this organ, and inasmuch as the condition in nearly one-half of such patients who come to the physician for examination is inoperable, there is room for some improvement in the matter of securing earlier recognition of the disease. At best, however, the gain will be comparatively small over present conditions, because in many instances the disease gives but few symptoms until it is far advanced, and because approximately 75 per cent of cancers of the stomach are so located or of such a type that early metastasis takes place into glands and into other organs, or the disease may become grafted throughout the peritoneum; to prevent this early operation is essential. About one-fourth of gastric cancers are confined to the stomach, and in this group if glands are involved they are in or connected with its wall without papillary outgrowth. These are the most favorable cases for operation, and yet all of this type are not operable

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for various reasons, advanced age, general debility, complicating diseases, or extensive involvement of the stomach. In the inoperable group may be placed the cases involving the cardia, approximating 10 per cent of the gastric cancers.

The literature concerning the general subject of cancer, especially of its etiology, is voluminous. Usually such articles are written with the object of proving special theories: for example, that cancer is or is not an hereditary disease, that it is caused by some unknown infection, or that this infection is water-borne, that it is due to malnutrition, general and local, and hence is a medical disease; that it is due to acids, especially of the sulphurous type, or to the excess of cholesterol. Cohnheim's theory of tissue displacement as a cause has long since been refuted. In taking a general survey of the various theories and reviewing the clinical evidence, it would seem that not one, but several conditions are essential to the development of cancer. The influence of heredity probably does not extend beyond an inherited cell weakness in which extra demand on the cell for division may early exhaust its controlling agent. The great influence of local irritation, which in some instances is undoubtedly chronic infection, is a fact quite generally accepted. No one theory, however, can account for the change in the cell that causes it to adopt lawless existence and to lose its harmony with community life. There is little change from the normal in the cancer cell, yet by the microscopic study of a group of cells and their relationship to surrounding tissues, cancer can be identified positively. An acid condition in the surrounding fluid also seems essential to cancer activity. Hot drinks are probably a cause of no little importance in producing cancer of the stomach.<sup>1</sup> Chronic ulcer is the most important factor to be considered in these cases, as in more than 40 per cent there is a history of ulcer varying from many months to several years before the onset of cancer. When seen early such cancers are found to have developed on the margin of an ulcer. In such location the demand of cell renewal is constant; when some cell exhausts its controlling granules in the division, and, reverting to single cell type, becomes parasitic, we may have the beginning of cancer, but only if other factors are present. The type and growth are dependent on the basal cell and the environment. In a general way it may be said that the nucleus is proportionately larger in the cancer cells, and is ready for division with less than the average amount of cytoplasm surrounding it. Individual cells, as well as groups, must

be studied. The various parts of the cell, taking different colors through the varying action of stains, show the complex chemical structure of the protoplasm. It is within reason to assume concerning the normal division of a cell that its control is the centrosome; possibly other granules may serve this purpose. Cell growth in cancer is undoubtedly stimulated by acidity or greatly lowered alkalinity. In this connection it is of interest to mention the work of Loeb. He found by a brief immersion of the unfertilized eggs of sea urchins in a 1 per cent solution of butyric acid and sea water, that the eggs became fertilized and took on active growth, without sperm. On the other hand, it has been shown that eggs of certain types of lower animals that develop in water, when placed in 0.6 per cent saline solution develop with frequent anomalies, especially of the higher nervous system, the last addition in evolutionary life.

The greatest number of cancers come in the area of highest acidity, the stomach. Ninety-eight per cent of intestinal cancers are in the colon, while cancer in the small intestine is relatively rare—about 2 per cent. Cancer in the urinary bladder is not uncommon, while in those organs with a limited period of activity, such as the breast, uterus, and prostate, a normal degeneration often becomes a pathologic one, the stimulating influence probably being of a chemical nature. Cancer of the duodenum is exceedingly rare, yet ulcer of the first portion of the duodenum is nearly four times as frequent as ulcer of the stomach, and while there is opportunity for involvement by continuity of tissue from the most frequent site of cancer in the body, the stomach, this does not occur. Ulcers appear in the first portion of the duodenum as it is bathed by the acids of the stomach before they are neutralized by the secretion of Brunner's glands; ulcers do not appear in the alkaline portion of the intestine below the common duct, although they may be found in a gastrojejunal opening which has there been rendered acid.

While I am not presenting this subject from the standpoint of diagnosis, I wish to refer to the progress which has been made in the diagnosis of gastric cancer, and to corroborate Carman's observations on the operability of cancer of the stomach as determined by the x-ray. Without the x-ray we would be back to the old methods of determining diagnosis, namely, by cachexia, loss of weight, achlorhydria, obstruction, tumors, and so forth, which are all signs of advanced gastric cancer. At a time when the cancer syndrome is not positive but probable, the

x-ray may be relied on to demonstrate lesions of the stomach in more than 95 per cent of the cases.

In general the treatment of cancer by radium is proving successful in certain types of the disease which can be reached by the ray; in some instances cure is produced and in others growth is delayed. By care and filtering processes the various rays are controlled. The effect on the cell is chemical, influencing the protoplasm or the local fluids. Radium is most effective in growths with active circulation, as it has a marked influence on the wall of the blood vessel. It also apparently acts on the cell nucleus, checking division, but it may be used to excess and cause local destruction. The x-ray acts on the cell protoplasm, checking growth, and it may also cause local destruction. Between these two conditions, the x-ray causes rapid epithelial proliferation, areas of which might at times be called precancerous. The cell, having lost its controlling granules through the ray's action and retaining its nucleus and cytoplasm, will become malignant when surrounded by the proper biochemic fluids. This shows that under certain conditions cancer can not only be produced but controlled. As yet radium and x-ray are only palliative or a means of delaying the progress of gastric cancer.

From Oct. 1, 1897, to Jan. 1, 1919, we performed 2094 operations for cancer of the stomach. Seven hundred and thirty-six of these were resections with a mortality of 13.7 per cent, 746 were explorations with a mortality of 2.9 per cent, and 612 were palliative operations with a mortality of 11.1 per cent. The common type of operation was the Mikulicz, Hartmann, Billroth No. 2, of which there were 359, with a mortality of 12.5 per cent. There were 19 of the Billroth No. 1 type with a 5 per cent mortality, 28 sleeve resections and 7 Kocher operations with a mortality of 14.2 per cent each, 115 posterior Polya operations with a mortality of 14.7 per cent, and 120 anterior Polyas with a mortality of 13.3 per cent. The local resections, 12 in number, gave the highest mortality, 25 per cent. These 660 resections have been done since 1906. Prior to this the type of resection was not described in the records definitely enough to be included in a statistical report. The Billroth No. 1 operation consists of a resection of the pyloric end of the stomach, and the suturing of the duodenum to the partially closed distal end of the remaining portion of the stomach. Since the Y-shaped line of suture of this type of operation frequently leaked, with fatal results, Billroth, with Mik-

ulicz and Hartmann, developed the so-called Billroth No. 2 operation, which consisted of completely closing the end of the stomach and making a posterior gastrojejunostomy. The Kocher operation avoids the

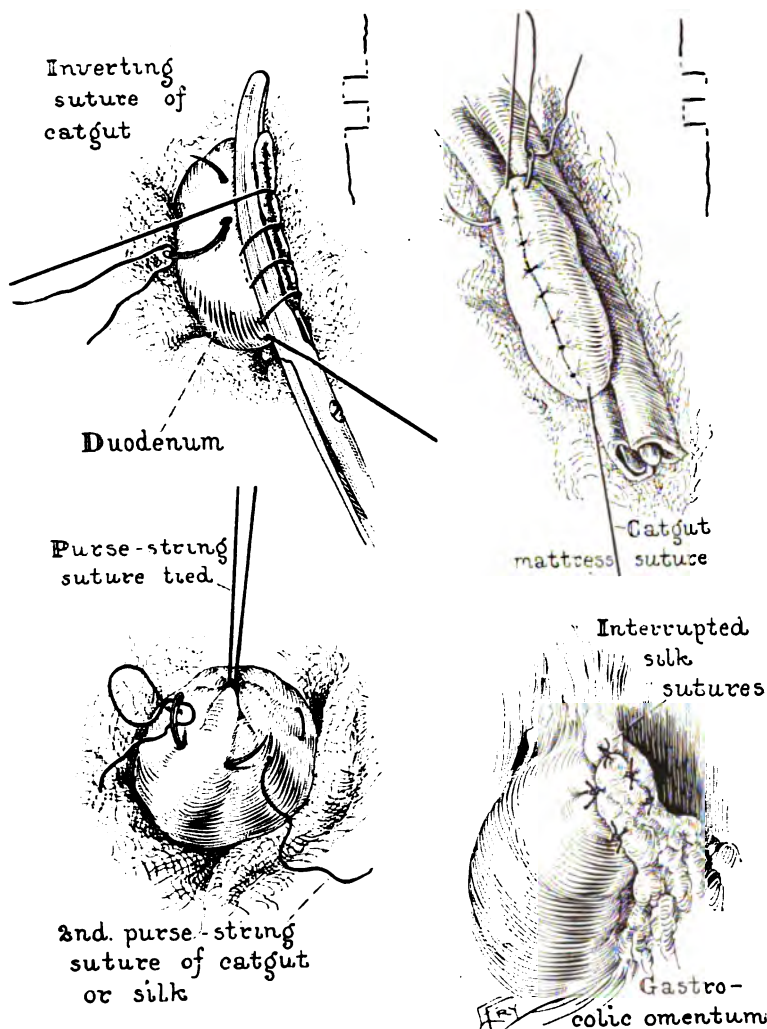


FIG. 28.—Two methods of closing and protecting the cut end of the duodenum.

leakage of the Billroth No. 1 operation by attaching the end of the duodenum through an opening in the posterior wall of the stomach after the open end is closed, but tension here occasionally gave obstructive trouble or leakage (Figs. 28 and 29). Polya avoided the double



operation of closure of the end of the stomach followed by gastro-enterostomy by uniting, retrocolic, the entire open end of the stomach to an equal sized opening made in the jejunum. In the Polya operation the newly formed end of the stomach consists of the jejunum, which spreads out as the stomach is filled; the opening may be from 3 to 5 inches in length, according to the size of the resected end of

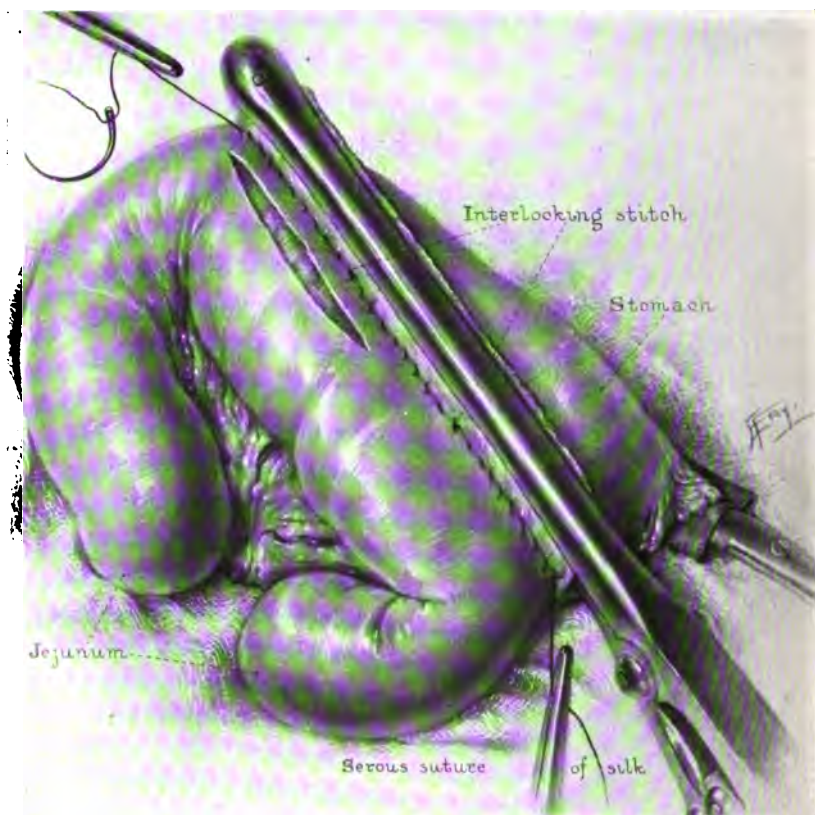


FIG. 29.—Jejunal attachment; approximate size of opening in bowel.

the stomach. If the opening is but 3 inches, the whole end of the stomach may be attached to the jejunum by incising the bowel a nearly equal distance; with each passing of the needle, the suturing loops catch a somewhat greater amount of the wall of the stomach than of the bowel. Since the bowel becomes the stretched-out end of the stomach with an opening at each side of the attachment, proximal and distal, the delivery of gastric contents is not so well accomplished

as it is with the partially closed end of the stomach with an ordinary sized gastro-enterostomy opening properly placed (Fig. 30). The

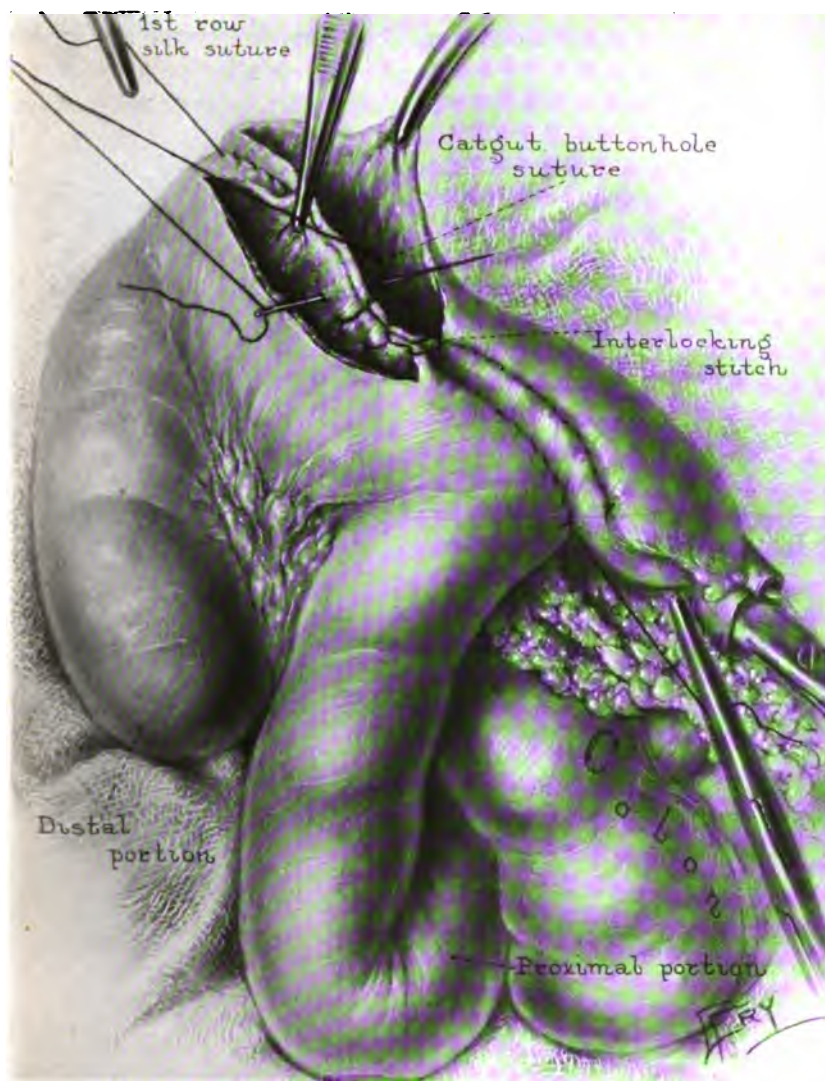


FIG. 30.—Gastro-enterostomy opening with partially closed end of the stomach.

mortality rate incident to the various operative methods is nearly the same; there is, however, some difference in the comfort and post-operative condition of the patient. In the operation described here-

with this large opening is avoided by attaching the jejunum to the posterior wall of the stomach close to the crushing clamps, which are left on to hold the stomach closed until the first row of sutures is applied. Before removing the crushing forceps the contents of the stomach are controlled by applying long, flexible rubber-covered forceps, slightly higher on the stomach, which prevent its contents

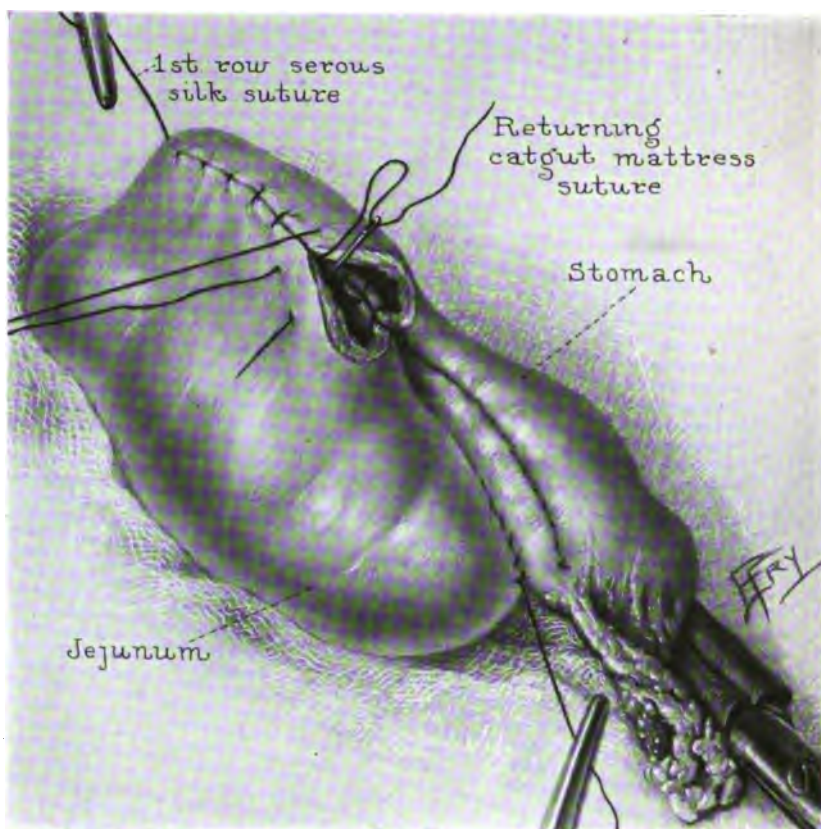


FIG. 31.—Catgut suture closing gastrojejunal opening and continuing over the closed portion of the stomach to reinforce the suture line.

from soiling the wound. After the first row of sutures has been made and the crushing forceps removed, the stomach is partially closed by an inturning suture, begun at the greater curvature, closing in toward the lesser curvature until the opening remaining is only slightly greater than the diameter of the jejunum. The jejunum is now opened opposite this point, a quarter of an inch from the first suture line, and



the ordinary technic of gastro-enterostomy is completed. The opening being closed, the suture is continued as a second row over the closed portion of the end of the stomach. The first suture is now continued over the anterior portion, making two rows on the gastro-enterostomy

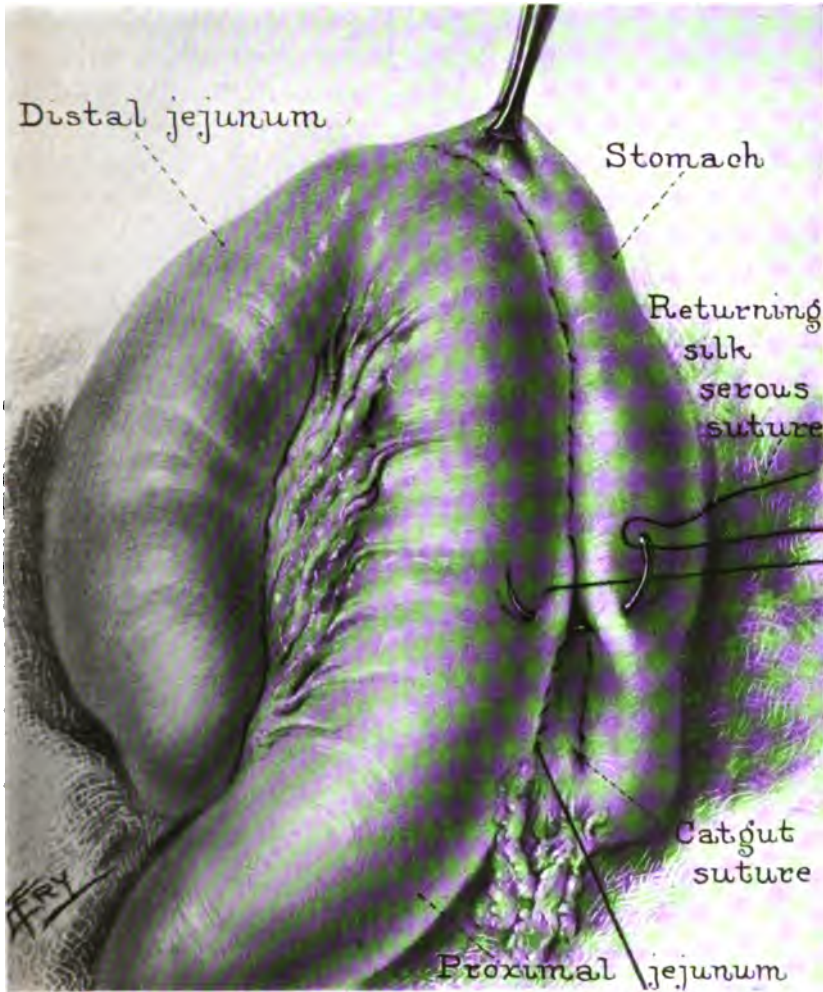


FIG. 32.—Final row, serous suture completing suture line which protects the end of the stomach with the intestine.

opening, and protecting still further the closed end of the stomach by suturing over it the unopened bowel (Fig. 31).

For the last three years we have been doing the anterior Polya, the

original Kroenlein instead of the posterior, bringing the loop of jejunum over the transverse colon. We abandoned the posterior Polya because of primary obstructive complications due to adhesions, to tension from gastric traction, or to late trouble from recurrence of the malignancy, with early obstruction. The anterior operation gives an easier convalescence on the average (Fig. 32). I believe that better after-results are secured by turning the bowel to the right, isoperistaltic, which was

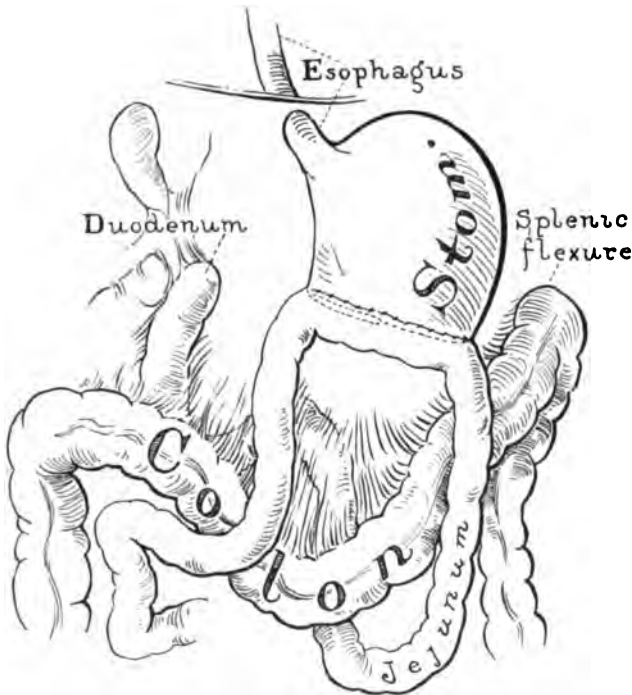


FIG. 33.—Schematic diagram. Method of attaching jejunum and stomach. Omentum not shown.

a marked feature in the earlier operations of anterior gastro-entrostomy. The point of attachment of the jejunum is approximately fourteen inches from its origin, while the opening in the stomach comes directly over the descending leg of its loop, the reverse of the Mikulicz partial closure and button anastomosis. The transverse colon naturally sags in its mid portion; by turning the bowel from left to right it is brought to the left of the center, while the stomach delivers along its lesser curvature the more fixed portion of the viscus. Inasmuch as the tissues of the stomach are more or less devitalized by disease

and more so by the operation, the suture material recommended is silk for the outer row and chromic catgut for the inner row; the silk guards against separation from delayed healing (Fig. 33). The completed operation can be made within one hour.

Our data bring the results of operation up to Sept. 1, 1917. Four hundred and twenty-seven patients were operated on during the three years previous to September, 1917. Those who died in the hospital and those not heard from number 121. Those who recovered from the operation and who have been heard from number 306; 115 (37.6 per cent) of these show three-year cures. Three hundred thirteen patients were operated on during more than five years before Sept. 1, 1917. Those who died in the hospital and those not heard from number 79. Those who recovered from the operation and who have been heard from number 234; 59 (25 per cent) of these show five-year cures. This is a most satisfactory showing for the surgical relief of an otherwise hopeless condition which is attended by much suffering.

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## DIAGNOSIS OF LATE RECURRENCES FOLLOWING GASTRO-ENTEROSTOMY: A PRELIMINARY RE- PORT ON 84 CASES OF GASTROJEJUNAL ULCER\*

G. B. EUSTERMAN

This subject is of particular interest because the determination of factors underlying late sequelæ is, under certain circumstances, the most difficult of gastro-enterologic diagnosis. Representative of these disappointments after surgery is gastrojejunal ulcer, a considerable number of which have gradually come under our observation, and which I have reviewed in the latter part of this paper. The subject matter incidentally affords the internist an opportunity to express certain convictions on an important phase of surgical therapy, both with regard to its virtues and its shortcomings.

That the ultimate results of the surgical treatment of ulcer-bearing patients is not uniformly successful is generally known, and conceded by the surgeon,<sup>7,8,9,11</sup> yet everything considered, there is no cause for serious apprehension on the part of our surgical conferres, notwithstanding the tenor of certain current contributions on the subject or the disheartening percentages of surgical failures advanced in discussion. Much of the criticism of surgical end-results seems to have been inspired and therefore unfair, while in other instances it was constructive in that the medical man, while admitting his own as well as the surgeon's share in the therapeutic failure, proposed remedial measures to circumvent the latter. It has been my experience that fair criticism is always welcomed by the rank and file of the surgical profession who are always open to conviction, invariably ready to adopt any procedure the efficacy of which has been proved to them. It is not within the province of this paper to discuss the relative merits of purely intensive medical or surgical treatment; the ulcer problem, however, is generally medical both before and after operation, but under certain conditions it is always surgical. There is a definite middle ground on which the internist and the surgeon can always meet, to

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say nothing of the many instances in which they might pool their therapeutic resources. The extreme views as to treatment too freely expressed by representatives of both factions only serves to delay that rapprochement so necessary to the best interest of the patient.

My observations have convinced me that the so-called medical treatment of ulcer has been incomplete, haphazard, and largely aiming at symptomatic relief in 90 per cent of the patients. Naturally a permanent cure is rarely achieved. In the minds of many medical men, including surgeons, such results unjustly condemn the method, both in practice and principle. As a consequence many patients become decided "chronics;" they often suffer from severe relapses and complications, and eventually seek relief in surgery. A gratifying majority are permanently cured or markedly improved thereby, without any recourse to other measures or restrictions.<sup>6</sup> There remains a considerable number, classified as improved and unimproved, including those with late serious sequelæ, which could be reduced appreciably by proper medical management. I believe that the surgeon in the past has too often stood in the way of his own success.

Good results in the treatment of many chronic ambulatory diseases often depend on the coöperation of the patient and his ability, through proper training by the physician, to treat himself. Familiar examples are the diabetic and tuberculous patient, the salutary effect of whose management and intimate instructions in hospital or sanatorium cannot be gainsaid. In the past few years marked immediate and remote beneficial effects have been recorded in several hundred gastro-enterostomized patients who have been instructed in those essential details regarding the nature and preparation of their food, habits, symptoms, proper use of alkalies, and other equally important measures.

Immediate and remote factors frequently unfavorable to ultimate surgical success are always present. Flint and others have shown that the anastomotic area is the site of a healing ulcerated surface for a period of fourteen days and that this healing is not always complete at the end of that time. It is now generally conceded that ulcers of the stomach and duodenum are largely embolic infections from some distant focus of infection. In other words, the presence of an ulcer should be considered good evidence for the existence of a remote focus of infection.<sup>12</sup> Finally, hyperacidity and hypersecretion, pylorospasm, and disturbed motility are known to make their reappearance by virtue of temperament, dyscrasia, vagotony, or



indiscretion, and to work mischief sooner or later. Such a situation has a peculiar appeal to the internist rather than to the surgeon, and it is successfully met by a carefully supervised immediate postoperative diet, devoid of premature, bulky, traumatizing elements, by the intelligent routine removal of provocative foci in teeth or tonsils, and finally by a later graduated system of diet, alkali therapy whenever indicated, and attention to other individual details. These are measures which prevent distressing functional disorders and subsequent formidable sequelæ. Skepticism on the part of the profession regarding the capacity for healing and the correction of vices of secretion through painstaking medical management, which includes the removal of foci of infection whenever indicated, is based on ignorance and prejudice rather than on fact.

Certain trends in present day gastric surgery give reassurance that many of the shortcomings and errors of the past which have on occasions reflected discredit will not obtain in the future. Chief among these are the disinclination to operate first and to diagnose afterward; to eradicate the ulcer-bearing area whenever possible; to refuse to operate on the stomach in the absence of a "visible, demonstrable and palpable lesion,"<sup>11</sup> and to explore routinely and remove any diseased organs of the accessory digestive tract. Under the latter circumstance surgical procedure has an inherent advantage in some cases in which gallbladder and appendiceal disease frequently co-exist with ulcer, and in which operation is primarily performed for a supposed ulcer, and the cause of the painful indigestion is found to be reflexly engendered by gross disease in one or both of the other organs. Obviously no form of medical treatment could permanently relieve the latter situation.

The immediate complications following gastrojejunostomy, such as hemorrhage, vicious circle, acute dilatation, and so forth, will not be discussed here. A perfected technic makes such features increasingly rare, but I shall very shortly consider more fully those causes giving rise to late, painful recurrences, identical with, or similar to, the pre-operative symptoms. However, the various reasons for disappointment or failure after gastro-enterostomy should be stated since they must be considered in arriving at a diagnosis, especially if the operation was performed elsewhere. Such causes may be classified as follows:

1. *Operation performed in the absence of a lesion intrinsic to the stomach or duodenum.*—In this group would be included the functional

gastric disorders which occur in neurotic and asthenic persons, ill-defined disturbances of the autonomic nervous system, including nervous vomiting, pylorospasm, instances of visceroptosis, achylia simulating the ulcer syndrome, atonic and dilated stomach, gall-bladder disease, appendiceal dyspepsia, gastric crises of tabes, splenic anemia of various grades, often associated with hematemesis and melena, hepatic cirrhosis, hyperplastic tuberculosis of the intestines, epigastric hernia, prolapse of the right kidney, and colonic adhesions and membranes.

The so-called functional cases, those in which no evidence of a pre-existing ulcer was found and in the majority of which no other intra-abdominal disease was noted easily constitute more than two-thirds of the surgical failures. This is evidenced by the fact that my surgical colleagues have undone more than 300 gastro-enterostomies performed elsewhere, as well as some of their own of an early period. I might add, that some neurotic persons with actual lesions either of the stomach or of the accessory digestive organs fail to improve after skillful surgical interference because their trouble was primarily of neurotic origin; also that an atonic, flabby ulcer-bearing stomach, usually found in an asthenic person, continues to give trouble after operation.

2. *Errors or defects in technic.*—Chief among these are: a stoma that was made too large or too small, or improperly placed; a long jejunal loop; improper application of jejunum to stomach so that the direction of the proximal short portion of the jejunum is from left to right; a kink or angulation in the efferent limb of the jejunum, or obstruction to the proximal loop; hernia of the small intestines into the lesser cavity; and the use of unabsorbable sutures. Some of these fortunately rare surgical shortcomings are sooner or later followed by symptoms alarming enough to make a secondary operation imperative.

3. *Lack of thoroughness in operating.*—An example of the lack of thoroughness in operating is the failure to remove a diseased gall-bladder or appendix at the time of an otherwise successful operation. If the patient's condition warrants it some authorities believe that it is expedient to remove the appendix in all abdominal operations. Failure to deal directly with the ulcer by cautery or knife excision, or at least by enfolding, will not insure against reactivity in the ulcer and the result will be a recurrence of original symptoms, especially hemorrhage.<sup>1, 2</sup>

4. *Late complications.*—To the group of late complications belong the cases in which the recurring trouble is chiefly of a painful nature, usually identical with or similar to the original symptoms for which the patient sought relief. The onset of such symptoms may follow soon on the operation, or they may not appear for a number of years, or the original symptoms, somewhat abated, may have continued since operation. The four main underlying causes are gastrojejunal ulcer, reactivity in the original partially healed or unhealed ulcer, carcinomatous changes in a chronic gastric ulcer, or the formation of a new ulcer in the duodenum or stomach. To a lesser degree, adhesions in the region of the pylorus from natural causes, or as the result of too much manipulation or repeated operations, cripple gastric function and provoke distressing symptoms. It is in such types that the greatest difficulty is encountered in determining the factor or factors underlying the complaint. This is especially true in the early stages of the trouble when thorough medical or surgical treatment promises the most, and when combined clinical and laboratory diagnostic procedure is not sufficiently informative. Successful differential diagnosis presupposes a thorough knowledge whenever possible of symptoms and conditions existing before operation, during operation, and after operation, especially with reference to whether or not an ulcer actually existed, gastro-enterostomy was done, or some procedure was carried out on the ulcer or pylorus. Any difficulties encountered during the operation, or immediate postoperative sequelæ, have especial significance. In the absence of reliable information the physician is thrown on his own diagnostic resources. In the examination special attention is paid to hyperacidity and hypersecretion, gastric motility, nine and twelve hours after a Riegel meal, blood in gastric extract and feces, palpable masses, and visible peristalsis. The barium motor meal and fluoroscopic examination are particularly valuable in visualizing new ulcers; this procedure occasionally gives reliable information with respect to the status of the original ulcer, of gastric motility, and of the roentgen ray characteristics of ulceration at the stoma.<sup>4</sup>

From a study of the postoperative condition of our patients in whom a definite ulcer was found and a uniform type of posterior no-loop gastrojejuno-stomy was done, with removal of any coexisting abdominal disease, I have drawn some general conclusions. As soon as the immediate effects of the operation have passed, the patient

experiences relief from the pain and associated symptoms suffered for a certain period after taking food, and an increase in weight and strength. This state of normal gastric function may continue thereafter without any special dietetic precautions. In a second group the patients may have periods of mild or moderately severe gastric disturbances from six to twelve months after operation; then without any definite measures for relief the symptoms subside permanently. Patients of a third group in whom a gastro-enterostomy is done for uncomplicated duodenal ulcer associated with hyperacidity, hypersecretion, and active peristalsis have a recurrence of the original trouble, and routine re-examination fails to reveal any organic cause. The inference follows that the old ulcer has become reactivated. Proper diet and alkali therapy, the removal of foci of infection, and the correction of bad habits cause marked amelioration or permanent relief of all symptoms. Pyloric occlusion, exclusion, or enfolding of the ulcer has not been successful. The slow progressive pyloric obstruction by a cicatrizing ulcer or inflammatory edema, or both, in an organ ripe for a gastro-enterostomy is a different proposition from a sudden artificial occlusion. Here should rightly be included and due allowance made for a considerable number who fail to get the relief they should from operation, and who belong to what might, briefly stated, be called the neurotic group. Many of their symptoms previous to the operation were of a character not easily explained by ulcer; their symptoms continue and are aggravated by an unstable nervous system reacting to the disappointment of not being cured. A smaller but interesting group of patients with similar clinical features present themselves after several years, at least, of complete comfort, and on examination or secondary operation are found to have a new ulcer in either duodenum or stomach (not a common occurrence), or a carcinomatous change in the primary gastric ulcer. We have record of 29 instances of the latter.

Gastrojejunal (pseudo-jejunal, jejunal) ulcer alone remains to be considered. It is to be remembered at all times that this formidable complication may be the cause of recurring symptoms early or late in the postsurgical period. In symptomatology it may differ little from the other causes mentioned, but its invariably progressive course, yielding slowly, incompletely, and frequently only temporarily, to careful medical management should arouse suspicion of its presence. Before considering this lesion more fully, some observations

regarding the postsurgical disturbances following pyloroplasty are pertinent.

The end-results following pyloroplasty in our cases have not been so satisfactory as the results following gastrojejunostomy, in spite of the favorable circumstances under which the operation usually was performed. The patients having a recurrence of trouble often complained as before, and frequently without demonstrable secretory or motor disturbance. In others gross retention was present beside pain and sensitiveness in the field of operation. Spasm, adhesions, and recurring ulceration in the operative field, single or in combination, are causes to explain the failure to restore health. Under any circumstance a secondary gastro-enterostomy gives prompt, permanent relief.

*Gastrojejunal ulcer.*—The two series studied are comprised of 84 cases, 48 of which followed gastro-enterostomy performed in the clinic for a benign gastric or duodenal lesion, and 36 followed gastro-enterostomy done elsewhere. Interesting observations on a large series of such cases have been made by von Key, Paterson, von Roengen, Lieblein, Moynihan, and others. W. J. Mayo and C. H. Mayo have contributed from time to time directly or indirectly to the subject, and more recently other contributions have been made from the clinic by Carman and Balfour, and Butsch, and others. I am reviewing the subject at this time primarily because of the considerable number of cases under observation and to call attention to the features that were prominent in the recognition of the lesion. To the present time about 3700 gastro-enterostomies have been performed in the Mayo Clinic for benign disease. During this time 48 gastrojejunal ulcers have come to operation. This probably does not represent all the gastrojejunal ulcers that have occurred because some have been operated on or treated elsewhere, and others are still giving trouble. It is also possible that some of these ulcers healed spontaneously after giving more or less trouble. Therefore, at least 1.3 per cent of all gastro-enterostomies are resubmitted to operation for ulceration at the stoma. In 98 per cent of these a posterior gastro-enterostomy had been done.

The second point of some significance is the fact that the ratio of the males to females in our entire series, including the series in which primary operation was performed elsewhere, was about 7 to 1; in primary benign gastric and duodenal ulcer the average ratio is about 3 to 1, so that many more males than females suffer from this condition

In a review of the clinical histories, some of which lacked essential details, four types of cases were recorded: (1) Cases with postoperative complaint almost identical with the preoperative history, (2); cases with a history of irregular ulcer, (3) cases of purely intestinal type with symptoms largely of pain and other disturbances referred to the lower abdomen, associated with bloating, occasional diarrhea, or severe constipation alternating with diarrhea, at times presenting a picture identical with that of intestinal obstruction; and (4) infrequent cases characterized chiefly by obstruction, perforation, or by a sudden onset of hemorrhage with or without a brief history of antecedent pain, not unlike conditions obtaining in a primary ulcer. The hemorrhage may or may not be repeated and is often first induced by unusual exertion or jarring. In a majority of our own cases the purely gastric ulcer type of syndrome sooner or later made itself evident, that is, the onset of pain after meals was earlier, and relief by the usual measures less distinct or brief in its effect. Relief by soda was more noticeable; nausea, vomiting, flatulency, nocturnal pain, loss of weight, and a more frequent repetition of the attacks were some of the predominant clinical features.

If gastrojejunal ulcer is suspected an idea of the pathologic process is often helpful in eliciting a more detailed history. This type of ulcer usually does not have a crater; morphologically it is more like the saddle ulcer of the stomach. It usually involves the distal segment of the anastomosis opposite the stoma and spreads superficially, especially over the gastric area neighboring the ulceration; the base of the ulcer is usually in the transverse mesocolon, involving the colon itself or rarely penetrating the colon, in the latter case forming a gastrocolonic fistula; or the ulcer may point outwardly with its base in the abdominal wall where the mass or the inflammatory thickening, or abscess, is apparent. Such a mass is more readily palpable if the anterior gastro-enterostomy is performed. Subacute or chronic perforation is a frequent complication. At times it is the cause of considerable pain or local soreness, tenderness or tumefaction. Pain on turning or twisting of the body, raising of arms, or during a lifting strain is usually evidence of adhesions involving the abdominal parietes. By virtue of the location of the gastrojejunal ulcer, the subjective pain and objective mass of tenderness are frequently lower than before operation.

In our series of 48 patients, 19 (40 per cent) definitely stated that their pain and soreness or tenderness were situated lower, in the

region of the umbilicus, than prior to operation. In 7 of these the postoperative symptoms were entirely left-sided. The incidence of hemorrhage was about the same as in the ordinary ulcer, 25 per cent. The presence of a tumor, mobile and usually non-sensitive, situated in the region of the navel, is of the greatest diagnostic importance, other things being equal.

Another feature influencing the symptomatology is the reactivation of the old ulcer, probably the result of disturbed motility and hyperacidity, or the occasional formation of a new ulcer. In our series this reactivation was noticed in 6 instances and a new ulcer was found in 2. In the 36 cases in which the primary operation was done elsewhere reactivation was distinctly noticed by the surgeons in 7, and probably in 9, or 25 per cent. The gastric analysis showed variable degrees of acidity; the average acid values showed a high normal acidity both for total acids and free hydrochloric. Hypersecretion was the rule and gross food or barium retention was present in about 25 per cent. Occult blood in the gastric extract was present in about 25 per cent. The time of onset of symptoms after operation was of interest. In our series 35 per cent had a recurrence of symptoms within six months; 56 per cent within a year; and, including the patients who experienced only partial or no relief, 88 per cent were complaining within one year after the original operation. In the group operated on elsewhere the percentage was about the same; in 12 cases (33 $\frac{1}{3}$  per cent) there was no evidence of primary ulcer at the time of the second operation. This, among other factors, points to the inference that the cause of gastrojejunal ulcer is largely some defect in the operation itself. In 14 of the patients nonabsorbable silk or linen stitches were found hanging loose in the anastomotic area, and in 7 cases of our series linen thread seemed to be definitely responsible for the trouble. That this is not the sole cause is evidenced by the fact that gastrojejunal ulcer has been found on several occasions since the use of absorbable sutures, although the incidence promises to be considerably less on account of this method.

The x-ray findings are of primary importance and often render a diagnosis conclusive. Carman calls attention to various x-ray phenomena in the presence of a gastrojejunal ulcer, for example, deformity of contour about the stoma, exaggerated peristalsis, gastro-enterostomy not freely patent, barium retention, spasticity of the stomach, and so forth. In our series of 48 cases of which 40 underwent x-ray

examination an unequivocal diagnosis of gastrojejunal ulcer was made in 18 cases; incomplete but contributory evidence was found in 14 others. Therefore in a total of 80 per cent of the cases helpful or conclusive information was obtained from the x-ray. In 8 (20 per cent) the findings were negative. In 36 cases in which the primary operation was done elsewhere and in all of which fluoroscopy was done, the positive and contributory diagnosis was made in more than 55 per cent. A clinical diagnosis of gastrojejunal ulcer was made primarily or secondarily on an average of 75 per cent in both series of cases. The operative mortality was about 2.5 per cent. The patients cured and much improved in the 48 cases averaged about 35 per cent. In the 36 cases the cured or much improved were 25 per cent. One reason for this lower percentage of cures is that the patient is merely restored to his pre-operative condition after the gastro-enterostomy is cut off, or a pyloroplasty is done under unfavorable conditions. The immediate operative mortality was 5.5 per cent.

#### CONCLUSIONS

1. Gastrojejunal ulcer is a serious complication following gastro-enterostomy and occurs in from 1.5 per cent to 2 per cent of cases; 1.3 per cent of our patients have been submitted to a secondary operation.

2. The ratio of males to females is 7 to 1, which is two and one-half times greater than the ratio in primary benign ulcer.

3. The symptomatology closely approaches that of benign ulcer. The course is usually rapidly progressive, and in the majority of cases tends to assume that of the purely gastric ulcer type; or the symptoms may be purely of intestinal origin, of pyloric obstruction, perforation, or hemorrhage. Fistulous connection with the colon is infrequent. The lesion is refractory to medical treatment.

4. A palpable mass was present in 10 of 84 cases (12 per cent). This is of great diagnostic importance. Hemorrhage occurs in about 25 per cent. Pre-existing ulcers tend to reactivation, or occasionally a new ulcer forms. Marked twelve-hour retention of food indicates narrowing of the stoma, and pyloric obstruction because of strictures from healed ulcer or previous artificial closure.

5. The x-ray furnished reliable direct or corroborative evidence in 65 per cent of the cases. X-ray data in the later series are conclusive.



in a high percentage, denoting progressive accuracy by virtue of accumulative experience.

6. Gastrojejunal ulcer is caused chiefly by a mishap in the operative technic. In 35 per cent in which there was no evidence of ulcer prior to gastro-enterostomy, gastrojejunal ulcer had formed. Secondary causes are the use of nonabsorbable sutures, severe focal infection, and trauma soon after operation associated with hyperchlorhydria and stasis.

7. Cure or improvement following secondary operation is obtained in about 35 per cent of the cases.

8. Careful operative technic combined with immediate and continued postoperative intensive medical management should greatly reduce the incidence of this formidable complication. Medical participation under any circumstance in addition to the removal of foci of infection insures satisfactory surgical end-results.

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# AN EXPERIMENTAL STUDY OF THE EFFECTS OF DUODENECTOMY

## A Preliminary Report\*

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AND  
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The scope of this investigation of the effect of duodenectomy in dogs is twofold: (1) to determine whether the duodenum is absolutely necessary to life, and (2) to determine its rôle in the functioning of the gastro-intestinal canal.

From a practical surgical standpoint, duodenectomy is probably of very little consequence, although several partial resections have been performed satisfactorily. From the physiologic point of view, however, the operation is significant. The duodenum occupies a very important anatomic and physiologic position just distal to the stomach, and is seemingly intimately associated with the physiology of that organ, with special reference to its mechanism for emptying. The liver and pancreas discharge their secretions into the duodenum, which bears some relation to the manner in which these organs functionate. In addition to this, the duodenum itself elaborates a secretion and contains glands (Brunner's) which are found only in this part of the body. It is thus possible that the duodenum is of importance in the general physiology of the organism and plays a necessary part in the function of the gastro-intestinal tract and in digestion. It seems logical, therefore, to believe that the removal of the duodenum will produce noticeable effects, and that the compensation of the body to its removal will make possible an evaluation of its real importance.

The first experiments recorded in the literature of the removal of the duodenum were made for the primary purpose of attempting to determine the relative part the duodenum and pancreas play in the production of experimental diabetes, and not for the purpose of

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determining the function of the duodenum. The results of the experiments of this group of early investigators, Pflüger, Ehrmann, Lauwens, Minkowski, Cimatori, Tiberti, Rosenberg, and Bickel, may be grouped under definite headings. All the experiments were performed on dogs, with the exception of Pflüger's; some of his were done on frogs. The method of removing the duodenum varied. In no instance was a complete, normal reconstruction made. The continuity of the gastro-intestinal tract was maintained either by a gastro-enterostomy (Lauwens, Minkowski, Cimatori, Tiberti, Rosenberg, Bickel) or by an end-to-end anastomosis of the jejunum to the pyloric end of the stomach (Ehrmann, Tiberti). The bile and pancreatic secretions were taken care of by:

1. Ligation and complete occlusion of both ducts (Ehrmann).
2. Cholecystenterostomy and ligation of the pancreatic ducts (Minkowski, Tiberti, Rosenberg).
3. Biliary fistula and ligation of the pancreatic ducts (Cimatori, Tiberti).
4. Biliary and pancreatic fistulas (Lauwens, Bickel).
5. Transplantation of both ducts into the stomach (Ehrmann, Lauwens).

The results of these investigations were not very satisfactory. In most instances the animal died shortly after the operation; in only a few instances did it recover from the immediate effects of the operation. Two of the animals lived two weeks (Lauwens), one three weeks (Rosenberg), two four weeks (Minkowski), and one four and one-half weeks (Bickel). The final results of some of these experiments are incomplete.

Gaultier studied the effect of injury to the duodenal mucosa in animals, and Zak reported observations on the effect of caustics on the duodenum in man.

Matthews studied the effect of various types of experimental operations on the duodenum. The duodenum was not actually removed in his experiments. Stasoff, in a research on the effect of the removal of various portions of the gastro-intestinal tract, also removed the duodenum. None of his animals in which the duodenum was completely removed survived. He was able to keep one animal alive in which the portion of the duodenum distal to the entrance of the bile duct was resected.

Since the early investigators of duodenectomy were mainly inter-

ested in the relation of the duodenum to pancreatic diabetes, their data on the function of the duodenum and the effect of its removal are not complete. Most of the animals died shortly after operation, and in instances in which the animal survived the method was subjected to the criticism that not all the duodenal mucosa was removed.

It should be noted that experiments dealing with the short circuiting of any particular portion of the gastro-intestinal tract do not parallel those in which the same portion has been surgically removed. For that reason the experiments of Matthews should be classed with those on intestinal obstruction and not of duodenectomy.

Since our investigation was started, three articles on the subject have been published. L. R. and C. A. Dragstedt, McClintock, and Chase studied the effect of duodenectomy in two series of dogs. In the first series a two stage operation was performed, and in the second series a one stage operation. In the first series one animal lived twelve days, and in the second, one animal lived three months. None of the duodenectomized animals, however, appeared to keep in good condition.

Grey removed the duodenum in three stages, leaving an interval of several weeks between each stage. One of his dogs survived all three operations (complete removal of the duodenum), and remained in perfect health for eight and one-half months.

Moorhead and Landes also used a three stage operation for the removal of the duodenum. They were able to remove the entire duodenum and to demonstrate that dogs are able to live in perfect health after such a procedure.

Dragstedt and his collaborators clearly showed that a dog can survive duodenectomy, but their work is open to the same objections as that of many of the earlier workers, namely: The duodenectomy was complicated by a loss of pancreatic, and, in some instances, of biliary function. As they suggest, this probably was the cause of the failure of their animals to maintain health. The results of Grey, one of whose animals lived the longest after duodenectomy, and of Moorhead and Landes, prove that duodenectomy is compatible with life and perfect health in the dog for relatively short periods.

#### TECHNIC OF DUODENECTOMY IN DOGS

In the first experiments we attempted a two stage operation for the removal of the duodenum. However, as it was our intention to

make extensive studies of the gastro-intestinal tract and the various organs after duodenectomy, it was soon seen that by the time the second stage of the operation was performed the many adhesions would greatly complicate our studies. We attempted to devise a one stage operation by combining the two stage operation in one. We had a few successes by this method. One animal survived forty-one days, but in this case the pancreatic ducts were ligated.

On account of these unfavorable results a new method was developed, and two points were accomplished: (1) The duodenectomy could be performed quickly, and (2) all the other involved organs, such as the bile duct, both pancreatic ducts, the pancreas and the alimentary tract, were restored to correspond as nearly as possible to the normal state. Briefly described, the operation consists of four steps:

1. The dissection of the duodenojejunal fold, the mesoduodenum, and the lesser omentum, and the ligation of the blood vessels supplying the upper jejunum and duodenum.
2. The separation of the pancreas from the duodenum and the isolation of the major pancreatic duct and the common bile duct, together with the minor pancreatic duct.
3. The removal of the entire duodenum, with a portion of the proximal jejunum and the distal pyloric portion of the stomach.
4. The implantation of the bile duct and the minor and major pancreatic ducts into the jejunum.

The technic described was developed on the dog, and, with slight modifications, it was found to be adaptable to several other species. The operation could usually be performed on the dog within from one and one-quarter to one and one-half hours, never longer than two hours. Several of the animals died as a result of the operative procedures before we had developed our technic. Others died from the results of intercurrent disease. After our technic was fully developed, however, practically all the animals lived.

## RESULTS

Our results on dogs fully corroborate those of the more recent investigators. The animals quickly recovered from the operation and, with a few exceptions, have remained in excellent health. Their general condition has been good; their weight usually has increased or remained stationary. A few of the animals steadily lost weight

and strength after the operation. At necropsy, or at exploratory operation on these animals, a dilated common bile duct and marked infection of the entire biliary tract were usually found. Evidently the transplantation of the ducts did not restore a condition sufficiently normal to prevent infection.

Examination of the blood to determine the cell count, hemoglobin, carbon dioxid combining power, and hydrogen ion concentration did not reveal anything abnormal.

Examination of the gastro-intestinal tract by the roentgen ray, employing a standard barium meal, showed only slight deviation from the normal. In some instances, the barium left the stomach sooner than in the normal dog, probably because of the loss of the pyloric sphincter. At other times, it seemed that the emptying of the stomach was slightly delayed and that the course of the meal was a little slower, but in each instance this delay was not any greater than in some of the normal animals. In general, however, no difference was noted in the passage of the barium meal in the duodenectomized and in the normal dogs. Roentgenograms of the gastro-intestinal tract appeared normal. Future studies may show some effect of duodenectomy on the mechanics of digestion, but at present none have been noted.

#### DUODENECTOMY IN OTHER ANIMALS

Up to this time all experimental duodenectomies, with the exception of a few on the frog, had been done on the dog. At the suggestion of C. H. Mayo, we attempted to determine the effect of the operation on other species, particularly on the herbivorous and omnivorous animals.

The duodenum was removed from the cat. The operation is easily performed on this species. It is necessary to transplant only one pancreatic duct, that which enters in conjunction with the common bile duct, as the other duct is quite small.

The goat was selected as a suitable type of herbivorous animal. The operation is difficult in this species. The duodenum is long; the length of intestine removed measured about 90 cm. As the pancreatic duct empties directly into the common bile duct, it is necessary to transplant only the latter. The thin walls of the jejunum make the anastomosis quite difficult.

The hog was selected as an omnivorous type of animal. The

removal of the duodenum is very difficult in this species. As the bile and pancreatic ducts empty separately, two transplantations must be made. For expediency and in order to remove all the duodenum, as in operating on the dog, it was found best to section at the duodeno-jejunal juncture, invert the end of the jejunum, and unite the jejunum slightly more distally to the end of the stomach.

The duodenum was also removed from the monkey (*M. rhesus*), its anatomy being similar to that of man. It is necessary to transplant only one duct in this species, since the minor pancreatic duct can be ignored.

We now have ten dogs, one goat, and one hog from which the duodenum has been removed. One of the ten dogs was operated on six months ago. All the animals, with the exception of one dog, are in good condition.

#### SUMMARY

The investigation was undertaken for the purpose of determining the effects of the removal of the duodenum. A one stage operation for the removal of the duodenum was developed. The duodenum was removed from the dog, cat, hog, goat, and monkey. Careful studies on the dog did not reveal any noticeable changes following the duodenectomy. The animals remained in good condition. Examination of the blood showed it to be normal with regard to cell counts, hemoglobin, carbon dioxid combining power, and hydrogen ion concentration. The roentgen ray showed the course of a standard barium meal to be practically the same as in a normal dog. Experiments on the other species have been too recent to allow conclusions to be drawn, but it would seem that the removal of the duodenum in the hog is as innocuous as its removal in the dog. No data have been secured to show that the duodenum is of great importance in any of the species used. Future studies with particular reference to gastric secretion, and so forth, may give more positive results.

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## THE ROUTINE MANAGEMENT OF DUODENAL ULCER CASES\*

W. S. LEMON

For several centuries physicians have known of the presence of ulcer in the stomach, but it is only within the last hundred years that the condition has been known to exist in the duodenum (Travers). Abercrombie, in 1830, noticed that distress came not with food but with its passing from the stomach. Sibson, in 1857, discussed the early treatment. Bucquoy, in 1887, was able to make a diagnosis before hemorrhage or perforation and consequent death had revealed the cause and the nature of the ailment. From that time, stimulated by Moynihan's report, in 1900, of his first operation for duodenal ulcer, by Weir's presidential address on perforating ulcer of the duodenum to the American Surgical Association in the same year, and by Mayo's report, in 1904, the advance in knowledge of the subject was rapid and the interest all absorbing. It has been found that ulcer of the duodenum has a definite symptomatology and can be diagnosed with much exactness by a study of the anamnesis alone. Other methods of diagnosis have been perfected and have become so reliable that but few cases presenting symptoms—a few do not present symptoms—are mistaken.

The examination of a patient complaining of trouble referable to the stomach must be made most carefully. The study of the case demands the care commensurate with its importance, and should occupy a period of at least three days. The first day a thorough history is taken, not by help of "leading questions," but first by allowing the patient to talk freely of his complaint, then by direct questioning and, finally, by repeated review. This is done daily until all the facts are obtained and have been set down chronologically. A complete physical examination is also carefully made the first day. The blood pressure is taken to detect evidence of arteriosclerosis, which in the

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aged may cause abdominal pain, and the temperature and pulse are noted for evidence of infection. The pupillary reflexes, the size and equality of the pupils, the presence or absence of scars, the movements of the eyeballs, the condition of the nose, the presence of oral sepsis or of infected tonsils, the condition of the ears, especially with regard to bone conduction because of its bearing on luetic infection, are noted, and a systematic examination is made of the glands, the thorax, the abdomen, and of the pelvis, either by the vaginal or the rectal route. The weight, strength, tremors, rigidity of muscles, superficial and deep reflexes, sensation and station are observed and recorded. In cases of duodenal ulcer anatomic thinking is particularly necessary so that no detail may be missed, because a large number of seemingly unrelated factors may produce symptoms referable to the stomach.

On the first day the blood count is taken, and the sputum and the urine examined. If there are any findings on physical examination of the lungs, the chest is roentgenographed. Other special examinations are made, such as the result of the general examination and study may indicate.

On the second day a Wassermann test is made, and the stool is examined for parasites, pus, blood and occult blood by both the Weber and benzidin methods. The latter is a confirmatory test and is not looked on as essential, but when positive it adds to the evidence required.

The diagnosis is usually made on the third day. Confirmation may be accomplished in two ways: first, by the reaction to medical management and by continuing the study of the stool and of the gastric contents after meals by means of the Ewald or motor tests, and, second, by gastric analysis followed by fluoroscopic study and examination of roentgenographic plates of the patient. The latter is the method most used; it has proved entirely satisfactory. The remainder of the third day is devoted to the correlation of the impressions gained from the history and the observations made at examination with the findings of the laboratories and the evidence of the roentgenograms. Only by such correlation can a differential diagnosis be worked out and finally a certain diagnosis reached. Cheney endorses the complete and detailed examination; he says, "The old diagnostic combination of characteristic history, negative physical findings, and stomach contents showing hyperacidity can no longer be depended upon." Carman summarizes his opinion regarding such diagnosis in the words,

"In short, I believe that no diagnosis can be too strongly fortified, and that any gross discordance between the findings from all sources should make the examiner cautious in his opinions."

The patient whose several examinations agree perfectly in determining duodenal ulcer will be in early adult or middle life, more often a man than a woman. He will tell of trouble lasting for from ten to fifteen years, a distress coming on insidiously in "spells" of from a week's to a month's duration, at first rather slight, later impressed on his memory by increasing frequency and severity. The spells usually appear in the spring or the fall or when the patient is under heavy stress of physical or mental work and they may be aborted by rest. Frequently the patient will say that his trouble is without discoverable cause, certainly not due to any particular kind of food, indeed that food during the inactive periods can be taken without discomfort, that it does not cause pain but rather eases the pain during the attacks, and that it is the emptiness of the stomach which produces his distress. Many patients volunteer the information that food brings relief and that soda or hot water or lavage produces the same result. Later in the course of the cycle pains come on at two or three o'clock in the morning, and, because they are relieved by food, the patient keeps a cracker or a glass of milk at his bedside. He gives the usual symptoms of hyperacidity, such as heartburn, belching, waterbrash, nausea, and often pain before vomiting which continues during the spell; within a few months after each attack there is a return to normal strength and vigor. The patient may speak of complications such as faintness and giddiness coming on suddenly with succeeding pallor and accompanied by black stool and occasionally by hematemesis, of sharp and very severe griping pains, indications of early perforation or of the continuous distress of obstruction with cramping pain and frequent vomiting, due either to edema and swelling or, when the trouble has persisted for a long time, to scarring and narrowing of the pylorus. Such a history, combined with a physical examination showing tenderness in the epigastrium or just to the right of the midline, rigidity of rectus and increased epigastric reflex, a report of hyperacidity, excessive motility on fluoroscopic examination and deformity of the duodenal cap, makes a diagnosis of ulcer almost certain.

I have summarized, in Table 1, the results of observations made by Moynihan, Graham, Mayo, Eusterman, Beckman, and myself. These points in differential diagnosis are applied daily in my clinical work.

Only after consideration of the results of clinical, laboratory, and x-ray examinations can it be determined whether medical or surgical means should be advised. In a most painstaking and minute manner Sippy has outlined his method of medical management, worked out by long and extensive clinical experience at the Presbyterian Hospital in Chicago. He gives only six indications for surgical intervention.

1. Secondary carcinoma.
2. Perforation into the free peritoneal cavity.
3. Pyloric obstruction of high grade due to indurated tissue narrowing that fails to yield to medical management.
4. Perigastric abscess.
5. Hour-glass stomach.
6. Hemorrhages.

Sippy states that the cases of pyloric obstruction that do not yield to medical treatment embrace only 10 per cent of the cases of obstruction, that the remaining 90 per cent are due to "pyloric spasm, acute inflammatory swelling and in some instances local peritonitis, and that the obstruction disappears during the first two or three weeks under the influence of medical treatment." Operation is only infrequently necessitated by hemorrhage associated with duodenal ulcer. All cases not included in one of the six classes named are treated by medical management, the essentials of which are the maintenance of the absence of acid and consequently the prevention of corrosion. The details of the treatment, that is, the frequent meals, the alkali interval, the aspiration to determine acidity, the daily stool examinations, and the long preliminary confinement to bed, followed by many weeks of rigid adherence to the management, are too well known to require further comment. Sippy finds that:

1. Patients under medical treatment do well subjectively.
2. The management must be long continued and repeated.
3. Blood will disappear from the stool within ten days except in cases of malignancy.
4. The pains of obstruction, the nausea, and vomiting disappear within a few days except in cases of cicatricial stenosis.
5. Acidity can be maintained at whatever level is desired.

Since the surgical examination of these cases has proved that they heal spontaneously only in rare instances, the disadvantages in such routine treatment are manifest. In this connection Moynihan states, "Relief of an attack in a case of chronic duodenal ulcer is easy;

TABLE 1

	Duodenal Ulcer	Gastric Ulcer	Cholecystitis	Appendicitis	Carcinoma of Stomach
1. Sex.	More males than females, 77 to 23.		More females than males.		
2. Age.	Middle age: 25 to 45.	Middle age: 25 to 45.	Middle age: 25 to 45.	Any age—especially young adults.	40 to 60 years.
3. Duration of symptoms.	Stomach trouble for many years. Average time: 12½ years.	Stomach trouble for years.			For many years as in ulcer—60 per cent of our cases. Recent—6 months to 1 year no former gastric history.
4. Early symptoms.	Insidious—almost imperceptible; hard to remember details.	Insidious—almost imperceptible; hard to remember details. May be irregular.	Distinct recollection of first attack. Pain sudden and severe. Relief sudden. Subsequent soreness. Recovery within a few days.	Very irregular pain—either before or after meals.	Same as ulcers but without remissions.
5. Pain—onset.	2 to 5 hours after meals when stomach is empty.	One to two hours after meals.	Within an hour after meals or may be during a meal. Big meal may bring on colic.	Very irregular.	Pain with food and until stomach is empty. Very little pain before obstruction.
6. Pain—character.	Sense of fullness, distention, gnawing, burning. Terrible pain of perforation.	Sense of fullness, distention, gnawing, burning. Terrible pain of perforation.	Extreme lancinating, almost intolerable pain with shock, chill, distention, sweats, catch in breath. Diaphragmatic spasm.	Continued, wearying discomfort.	Aching; cramping in cases of obstruction.
7. Pain—duration.	Until next meal.	Shorter. Pain recurs before next meal.	Few hours to several days.	Indefinite.	Until stomach is emptied.
8. Accompanying symptoms and signs.	Appetite good. Constipation. Pain often relieved by pressure. Eructation of bitter food or gas with relief, 77 per	Fear of eating. Appetite not so good. Some pressure relief. Symptoms not so clear cut. Vomiting slightly more fre-	Nausea and vomiting (impacted stones, ulceration, or adhesions). Bile regurgitated mainly during attacks. Acidity and	Dilated colon with air gives pain over appendix. Appetite poor. Constipation. Character of food giving discomfort is vari-	Symptoms often begin with ulceration or obstruction. Cancer may be very large without causing symptoms of any kind referable

	cent. Water-brash, heart-burn, vomiting, 79 per cent. Loss of nutrition late in disease. Tenderness midline or to right. Rectus rigidity. Increased epigastric reflex.	quent, 82 per cent. More often food in vomitus. Gas more frequent, 94 per cent. Water-brash and heart-burn more frequent. Tenderness more to left and higher up. Loss of nutrition more frequent.	heart-burn sometimes present. Pain on pressure over gallbladder or liver. Gasping inspiration on deep palpation. Loss of nutrition except in cases of chronic jaundice or those with chronic pancreatic disturbance.	able with each individual. Vomiting frequent, gives relief. Gas troublesome. Often no pain over McBurney's.	to stomach. Weakness. Loss of appetite and weight with anemia. Palpable mass means cancer in almost all cases. Tender on pressure. Muscles often thin, relaxed. Absence of normal subcutaneous tissue. Signs of obstruction, peristalsis. Vomiting (sour, grumous food). Metastasis to supraclavicular gland of left side and to umbilical gland. Large liver. No referred pain, always in epigastrium.
9. Referred location.	Always epigastric—may be to right. Seldom goes to scapula.	Epigastric—central or to left, a little higher, radiating to left breast. Pain in back when pancreas is eroded.	Right costal margin into back, beneath right scapular angle (cystic duct pain). Tender on pressure, opposite 12th dorsal vertebra on right side.	Always in epigastrium—may be in either flank. Usually to right.	
10. Effect of food.	Food ease; patient eats between meals. Pain comes earlier with liquid diet.	Relief only temporary and occasional. Small meals give greater relief.	No relief, food is repugnant.	Food usually considered responsible.	Pain.
11. Effect of alkali.	Relief.	Relief.	No relief.	No relief.	No relief.
12. Effect of lavage.	Relief, especially in cases with complications, perforation, adhesions, obstruction.	Relief greater.	Relief during attack.	No relief.	Relief in cases of obstruction.
13. Effect of work or rest.	Often result of overwork or stress. Attack often aborted by holiday.	Often result of overwork or stress. Ease from lying down.	Sometimes result of work with movement of stones.	No relief from change of work or from rest.	Patients unable to work as weakness progresses.
14. Pain at night.	Patient awakened 1 to 2 a. m. Food for relief of pain kept by bedside.	Less frequent.	Not greater nor more frequent than in day time.	Not usual.	Constant.

TABLE I—Continued

	Duodenal ulcer	Gastric Ulcer	Cholecystitis	Appendicitis	Carcinoma of Stomach
15. Recurrence of symptoms.	Each day of attack a replica of preceding day.	Less constant.	Daily variation of symptoms.	Variable.	Constant
16. Incidence of symptoms.	Cramp-like pain only occasional.	Not seasonal, but similar periodicity. Continuous history, 10 per cent.	High.	High.	Pylorospasm present when food is in stomach.
17. Recurrence of "spells."	Spring and fall. May be sudden. Continuous history 4 per cent.	More irregular, more often not complete gastric ease.	At any time without reference to any known cause and without warning.	Rarely any intervals of comfort. Exacerbations of severe symptoms the only spells.	No spells.
18. Duration of "spells."	2 to 3 weeks or several months. Continuous with inflammatory or cicatricial obstruction.	Pain often continuous, and spells merely exacerbations.	Usually from 1 hour to several days.	One-half day to two-thirds day.	No spells.
19. Interval between "spells."	Complete return to health with gain of weight lost during spell. Patient may remain well months.	Lower. Obstructions by saddle ulcers or those near pylorus, 10 per cent. Lower because of thicker walls.	No orderly sequence of events.	Indefinite and indeterminate.	Depending on location; frequent with cancer if near pylorus.
20. Incidence of obstruction.	Vomiting 26 per cent; first symptoms may be with hemorrhage.	Lower because of thicker walls.	No.	No.	No.
21. Incidence of perforation.	25 per cent.	Usually not so profuse. May be copious and alarming. More often in vomitus.	No.	No.	Frequent small hemorrhage with coffee-ground vomitus.
22. Incidence of hemorrhage.	More often melena than hematemesis. Profuse and serious bleeding (faintness, weakness, breathlessness).	Occult blood found less frequently.	Very low.	Very low; may be melena.	Blood persists in stools after many days of medical treatment.
23. Stool examination.	Occult blood almost always found in cases of active ulcer.		Very rarely any hemorrhage or occult blood. Putty stool with dark urine when jaundice is present. Fat with pancreatic disturbance.	Melena may be present.	

24. Gastric analysis.	Hyperacidity during attacks, 70 per cent. (Continuous presence indicates an organic lesion.)	Not easily distinguished from duodenal ulcer.	Most cases normal. May be hyperacidity. Usually achylia in long-standing cases.	Usually hyperacidity.	Achylia. Barolin, Oppler-Bloss bacilli.
25. Roentgenographic examination.	Deformity of duodenal cap. Obstruction found better by x-ray than by residue from test meal.	Niche or filling defect.	Positive in only 10 per cent of cases. X-ray negative. Adhesion to duodenal cap causing deformity simulating duodenal ulcer.	Negative.	Filling defect often positive and may be diagnosed very early in the disease.

a cure of the condition by medical means, is, I believe, almost impossible." And again, "The lesion found is of such a nature that anything other than surgical treatment is not worth considering. It is safer, speedier, and more certain than any other mode of treatment."

After a period of serious symptoms lasting for some weeks the patient with duodenal ulcer may have complete relief, and yet, if operated on during the quiescent period, the ulcer will almost regularly be found open and unhealed. The supposed cures of chronic ulcers of the stomach and duodenum may be compared with the supposed cures following each attack of recurring appendicitis or gall-stone disease.

The unprejudiced observer, I believe, must come to the conclusion that operative relief in cases of calloused ulcers of the stomach and duodenum is indicated after a reasonable amount of medical treatment has failed to produce a permanent cure. It has been our experience at the Mayo Clinic that patients who have grown weary of being so often "cured" medically come for surgical help. At operations performed in many cases within only a few weeks of the completion of a rigid medical management, and at many operations performed during the remission of symptoms, an active ulcer was found. The remission in the latter case represents the "normal" resting stage; in the former it is artificially produced. It is our practice in the very recent cases to ask the patient to undergo medical treatment and to give the ulcer the best opportunity possible for spontaneous healing. Long standing ulcers, we believe, do not heal and should be surgically treated to remove the danger of hemorrhage and of perforation.



A comparison of the results of medical and surgical treatment may be gained from the following deductions:

1. Eighty-one per cent of patients with duodenal ulcer operated on at the clinic were so much relieved that they could be considered cured, and 10 per cent were markedly benefited (Graham).

2. Acidity is reduced by the mechanical hooking up of the jejunum with the stomach, because it allows the alkaline secretion of the duodenum to flow into the stomach and neutralize its acidity. (In the series of 200 cases I have studied this has been found to be universal and the average reduction in total acidity 39 per cent, in free hydrochloric acid 46 per cent).

3. If patients are to remain well they must have focal infections removed. Patients who are not improved or those with gastro-jejunal ulcer, except those in whom operative technic has provided a mechanical cause (Mayo, Carman and Balfour), usually show a high grade of neglected oral sepsis, even when most urgent advice had been given at the time of operation.

4. Operation reduces to the minimum the danger of perforation and of hemorrhage.

Because there are patients who do not improve when treated only by surgery, every patient should be advised with regard to postoperative care until permanent cure is assured. Acidity has been reduced mechanically; it may be kept at a minimum by medical management. Every patient should be informed after operation as to proper diet, the basis of which should be milk, cream, eggs, cereals, vegetables, purées, gelatin, scraped beef, bread and butter, jellies, custards, and creamed foods; later other lean meats and broths may be added. The patient's weight must be watched so that loss may be prevented and diet kept up to the bodily requirement. By such dietetic control and by the use of alkali in suitable doses the acidity can be accurately controlled when only three meals a day are taken. It is my practice, however, to advise a morning and an afternoon lunch, consisting usually of a glass of milk and a cracker, at least during the first few weeks of convalescence. This is productive of good results and will increase the chances of the surgically treated ulcer patients to regain and to maintain normal health. Only patients who were not given the usual advice have complained postoperatively. Operation for duodenal ulcer cures in most cases, and it improves in almost all. Clinicians must do their part by postoperative advice to help obtain the best results from the operation.

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## SURGICAL TREATMENT IN THE BLEEDING TYPE OF GASTRIC AND DUODENAL ULCER\*

D. C. BALFOUR

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The surgical treatment of uncomplicated benign lesions of the stomach and duodenum has reached a high state of efficiency and standardization. The various complications, however, which may develop in direct connection with gastric and duodenal ulcer, such as acute and chronic perforation, obstruction, deformity, malignant degeneration, and hemorrhage, present added problems to the surgeon; one of the most important of these is hemorrhage.

Gastric hemorrhage has been the occasion of more confusion in diagnosis, uncertainty in therapeutic indications, and irrationality in treatment, both medical and surgical, than perhaps any other gastric condition. The number of cases seen in which an erroneous interpretation of symptoms has led to incorrect suggestion for treatment, resulting in failure to protect the patient against further hemorrhage, illustrates the necessity of persistent study of the subject. This paper is concerned chiefly with two groups of cases: first, those in which operation has proved unsatisfactory because of error in attributing the bleeding to a lesion which is not present, and second, those in which the surgical procedure carried out has failed to obviate further hemorrhages, even though a correct diagnosis has been made.

A study of these groups disclosed certain facts which indicated that it should be possible to decrease the incidence of such failures; in the first group, by more accurate preoperative diagnosis, with better interpretation of operative findings; in the second group, by the addition of certain specific measures to the standard surgical procedures applicable to benign lesions of stomach and duodenum.

The first group of cases, those in which no intrinsic lesion is present, not only is large but also includes a variety of conditions which may be

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associated with hematemesis. Some of these conditions do not fall within the field of the surgeon, but there are other conditions which can be eradicated by surgical means, and this group is so important that I shall review briefly a representative example, a case illustrating the diagnostic error of presupposing gastric ulcer because of hematemesis, and of following the error by carrying out a routine operation on the stomach designed to cure this imaginary ulcer:

A man (Case 132411), aged 55, came to the clinic, June 5, 1915, because of recurring hematemesis. In some of the attacks the patient had been almost exsanguinated. The hemorrhages had begun in January, 1914, without a previous history suggestive of a causative factor; in July, 1914, a gastro-enterostomy was performed at his home; he was told that an ulcer was found at the pylorus. Some weeks after the operation a hemorrhage occurred similar to those he had had before the operation, and between that time and his registration in the clinic he had had several distinct gastric hemorrhages, the last severe one occurring in February, 1915. There were no typical symptoms nor physical or laboratory findings to establish a diagnosis, but the patient's condition and history were such as to make further exploration imperative.

In July, 1915, I explored and found a patent and well functioning gastro-enterostomy. Palpation revealed no induration in stomach or duodenum, and no visible signs of ulcer, nor did careful inspection through a large opening in the anterior wall of the stomach show any evidence of an active or healed ulcer at the anastomosis or in the stomach or duodenum. Exploration of the biliary tract disclosed a slight thickening of the walls of the gallbladder through which the yellowish spots on the surface of the mucous membrane which indicate a cholecystitis of the "strawberry" type could clearly be seen. The pancreas, too, showed very distinct changes, being considerably enlarged and nodular. This fact, the gallbladder findings, and past experience in similar cases, seemed a clue to the cause of the hematemesis. There were no recognizable changes in the liver, and general exploration was negative. A cholecystectomy was performed because in our experience with cholecystitis, with or without stones, associated with pancreatitis, and without jaundice, this has seemed the operation of choice. A well defined chronic catarrhal cholecystitis of the most typical "strawberry" type was found. The patient made an uneventful recovery and has had no hemorrhage since.

Similar cases in which the appendix, spleen or liver is the basic focus are not infrequently seen.

The first question, then, to demand a decision in cases of gastric or gastro-intestinal hemorrhage concerns the cause of the hemorrhage. Fortunately, in the majority of cases careful history taking, associated with expert interpretation of roentgen-ray findings, will usually determine whether or not an ulcer is present. If the evidence does not support a diagnosis of ulcer, but indicates disease in some organ in the abdomen, such as the gallbladder, pancreas or appendix, it

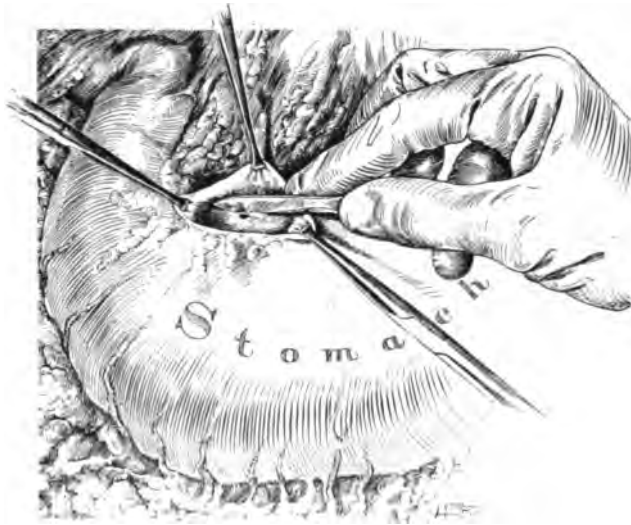


FIG. 34.—Shaving of thickened musculo-peritoneal coats.

must not be forgotten that gastric hemorrhage may be due to such extrinsic causes. The spleen and liver particularly should be kept in mind as causative factors, for it has been proved that either the spleen or the liver or both can be the cause of most serious gastro-intestinal bleeding without showing any changes that are recognizable in our present state of knowledge. The group of cases in which an undoubted gastric hemorrhage has occurred but in which the symptoms or physical findings are insufficient to lead to a positive diagnosis either of ulcer or extrinsic trouble requires, therefore, the most serious consideration as to whether operation should be undertaken. Fortunately, symptoms are usually associated with such hematemesis, and, though obscure, justify an exploration, and although doubt may exist as to

any satisfactory explanation being found to account for the hematemesis, frequently pathologic conditions extrinsic to the stomach are found which, when eradicated, secure permanent protection against further hemorrhage. In hematemesis unassociated with abdominal symptoms or findings, and in which it is not possible to establish a diagnosis, operative interference should, as a rule, be advised against.

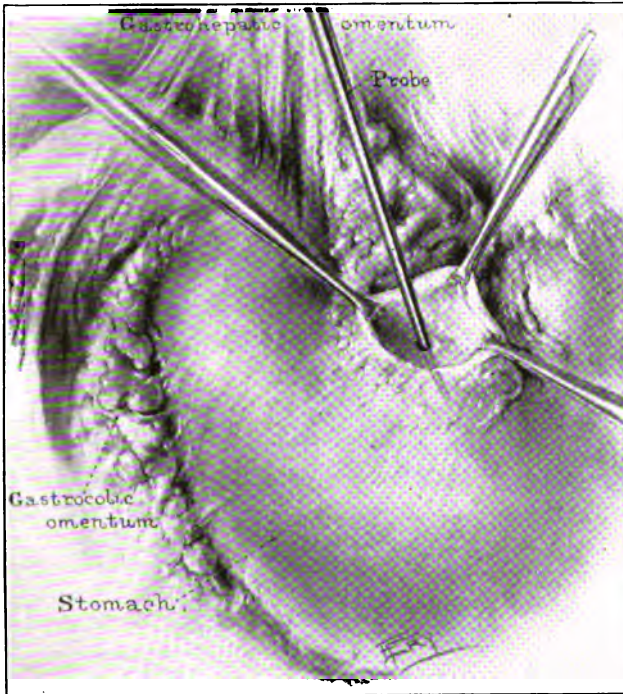


FIG. 35.—Probe introduced through the site of chronic perforation.

The group of cases, however, to which I particularly refer is that group in which recurring gastric hemorrhage has been caused by a chronic gastric or duodenal ulcer. Our records show that 25 per cent of gastric ulcers and 20 per cent of duodenal ulcers have been complicated by one or more gross hemorrhages. In the earlier days of gastric surgery the operation of gastro-enterostomy proved to be so efficient in a large majority of benign lesions of the stomach and duodenum associated with hemorrhage that the realization came rather slowly that at least some of the failures to obtain a complete cure, including protection against further hemorrhage, could be attributed to the

fact that direct attack on the ulcer was not added to the indirect therapeutic measure of gastro-enterostomy. The recognition of the danger of malignant degeneration in gastric ulcer gave the first impetus to the practice of combining gastro-enterostomy with the radical excision or destruction of such ulcers. The advisability of such a principle is now well established.

It has, therefore, become quite evident that in the surgical treatment of a gastric or duodenal ulcer which has been the cause of hemorrhages, some direct attack on the ulcer is most important. The necessity for this has become apparent to us because of the fact that a number of our own patients with duodenal or gastric ulcer had failed to secure, by gastro-enterostomy alone, protection against further bleeding. Apparently rare as such failures were, they nevertheless formed in the aggregate a group which called for an investigation as to the possibilities of reducing the number of such recurrences. A concise compilation of such cases illustrating the incidence of hemorrhage as a late postoperative complication may be found in the accompanying tables. The cases chosen for study were those in which operation was performed in the Mayo Clinic during the twelve year period between January, 1906, and January, 1918.

A study of Table 1, which represents the percentage of hemorrhages following operations for duodenal ulcer, shows that 12.7 per cent of

TABLE 1.—HEMATEMESIS IN CASES OF DUODENAL ULCER IN WHICH OPERATION WAS DONE

Jan. 1, 1906, to Jan. 1, 1918

	Cases, No.	Per Cent	Operative Mortality from All Causes, Per Cent
Total number.....	2875	....	1.6
Patients having hemorrhage before operation....	583	20+	1+
Patients having hemorrhage before operation heard from.....	494	86.0	
Patients reporting hemorrhage after operation....	63	12.7*	
Patients reporting hemorrhage after operation but none before.....	20	0.9	

\* Or 2 per cent of the total number.

the patients who had hemorrhages before operation had hemorrhages after operation, and in two instances the hemorrhages were sufficient

to cause death. Twenty patients (0.9 per cent) in the group who had not reported hemorrhages before operation had hemorrhages following operation. Eighty-three patients, 2.8 per cent of the total number operated on, had hemorrhages following operation:

Fifteen patients (8 per cent) with gastric ulcer report hemorrhage after operation who had had hemorrhage before, and two patients (0.3 per cent) had hemorrhage who had not had hemorrhage before operation. Seventeen patients, therefore, suffered from hemorrhage after operation, a percentage of 1+ of the total number of gastric ulcers operated on.

A comparison of the figures in Tables 1 and 2 shows that the incidence of hemorrhage in duodenal ulcer following operation is definitely higher than the incidence in gastric ulcer, notwithstanding the fact that there is a greater tendency for gastric ulcer than for duodenal ulcer to be complicated by bleeding. This important fact, namely, the difference in operative results in gastric and duodenal ulcers, may be largely attributed to essential differences in operative technic.

The radical treatment of gastric ulcer was originally due to the recognition of the fact that an ulcer on the gastric side of the pylorus holds unquestionable possibilities of becoming malignant. Excision of such ulcers either by knife or cautery was, therefore, performed whenever possible by surgeons whose experience was sufficient to make them appreciate the necessity of this treatment. Such radical measures necessarily carry a higher operative mortality, but the avoidance of such mortality by simpler operative measures means a marked increase in ultimate morbidity and mortality.

In duodenal ulcers, however, radical treatment was not necessary because of this possibility of malignant degeneration or of disabling complications, and the indirect method of treatment by gastro-enterostomy proved to be sufficient in a high percentage of cases to relieve the patient of the symptoms of which he complained. The more frequent occurrence of hemorrhage after operation for duodenal ulcer than for gastric ulcer is apparently due to this difference in operative procedure, and the following facts bear out such a statement: In not one of the 83 cases in which hemorrhages occurred after operation for duodenal ulcer was the combined operation of excision of the ulcer with gastro-enterostomy carried out, and with the exception of 8 cases in which various types of pyloroplasties were per-



formed, in every case a gastro-enterostomy alone was performed. This fact is significant particularly when one compares the results of the established methods of excision and gastro-enterostomy in gastric ulcer in which, although the tendency to hemorrhage had been greater, a much smaller percentage of bleeding followed operation.

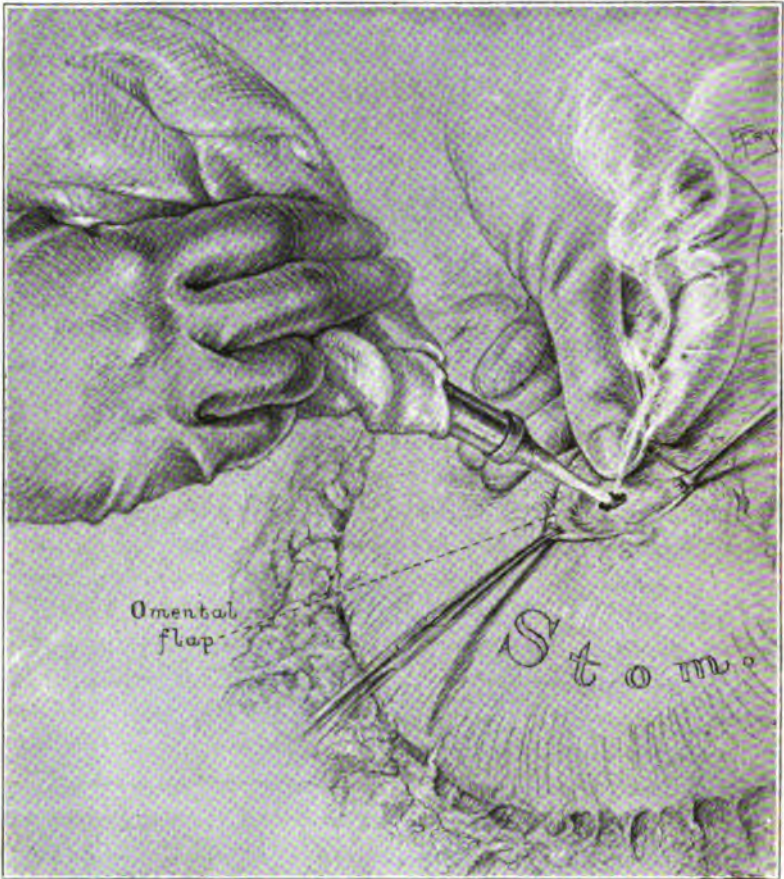


FIG. 36.—Peritoneal surface of ulcer prepared for application of cautery.

The combined procedure of excision and gastro-enterostomy was carried out in only one of the 17 cases of gastric ulcers in which there was bleeding after operation. These facts can only mean that the methods of direct attack combined with gastro-enterostomy which are used in the treatment of gastric ulcer are a source of protection to the patient against further hemorrhage.

TABLE 2.—HEMATEMESIS IN CASES OF ULCER OF THE STOMACH IN WHICH OPERATION WAS DONE

	Cases, No.	Per Cent	Operative Mortality from All Causes, Per Cent
Total number.....	863	....	3+
Patients having hemorrhage before operation....	222	25.8	4.8
Patients having hemorrhage before operation heard from.....	180	81+	
Patients reporting hemorrhage after operation....	15	8.0*	
Patients reporting hemorrhage after operation but none before.....	2	0.3	

\* Or 1+ per cent of the total number.

Another point brought out in the study of these cases is that in the majority of those patients who had bleeding after operation, the operation relieved all other symptoms, so that the recurrence of the complication of hemorrhage was the only feature which marred an otherwise perfect result. This fact is difficult to explain. It raises the question, for example, whether the hemorrhage actually comes from the site of the symptomless ulcer. The fact that the mucous membrane can bleed when no visible lesion is present, and that recurring hemorrhages from the stomach may take place without any demonstrable changes either in the stomach or in any other organ, throws some doubt on the assumption that all such recurrences have their origin at the site of the ulcer. But the fact remains that in the majority of cases in which we have reoperated, radical treatment of the ulcer area obviated further hemorrhages.

Our gradual realization of these facts, particularly when we found that 12 per cent of duodenal and 8 per cent of gastric ulcers which had been the source of bleeding before operation bled after operation, led to a thorough search for some means of lowering the incidence of these failures. From a study of our own cases it was perfectly evident that gastro-enterostomy alone, as I have pointed out, is insufficient protection against further hemorrhages, and that excision combined with gastro-enterostomy has given almost total protection. The problem resolves itself, therefore, into one which concerns the safest method of accomplishing a radical excision in the majority of cases. Various suggestions have been made and carried out at different times.

Ligation of the vessels in the circumference of the ulcer, a procedure highly recommended by Woolsey, devitalization by constricting suture, pyloric exclusion of von Eiselsberg, and excision have all been tried. Unfortunately, under certain circumstances knife excision is

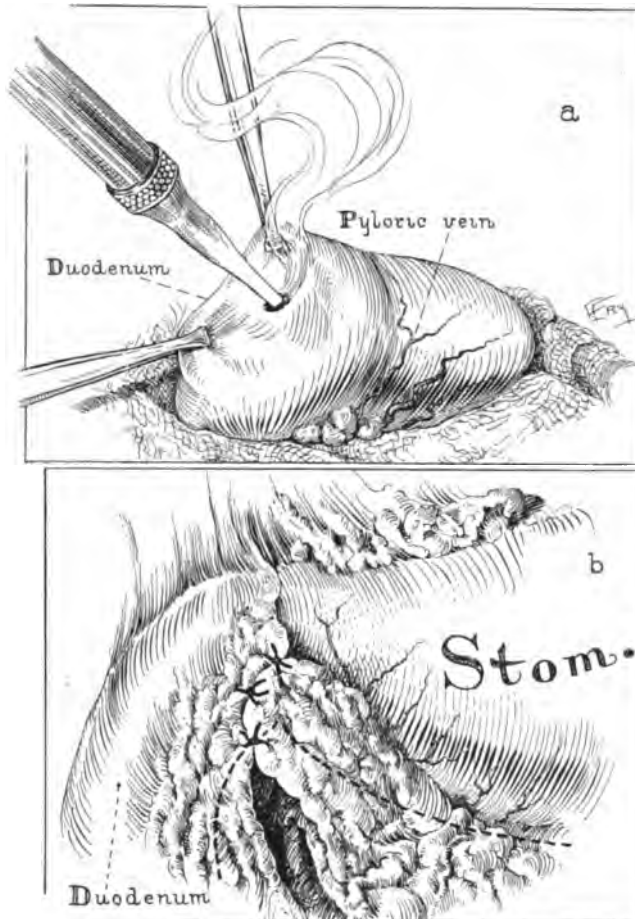


FIG. 37.—a, cautery puncture over a small duodenal ulcer; b, completed operation; omentum implanted over site of closure.

a formidable technical procedure and one at which even the experienced surgeon will wisely hesitate. In a search for some method which will be at the same time radical, safe and applicable in the largest number of cases, we have adopted the actual cautery as meeting these requirements.

## TECHNIC

The technic for the use of the cautery in the bleeding type of gastric ulcer differs in no particular from that used in the ulcer which has not been associated with bleeding; it may be briefly described by stating its important features.<sup>2</sup> Probably the most important point in the technic is the exposure of the peritoneal side of the ulcer, and, in a great many instances, as we have recently demonstrated, a close shaving of the gastrohepatic omentum (Fig. 34) with a portion of

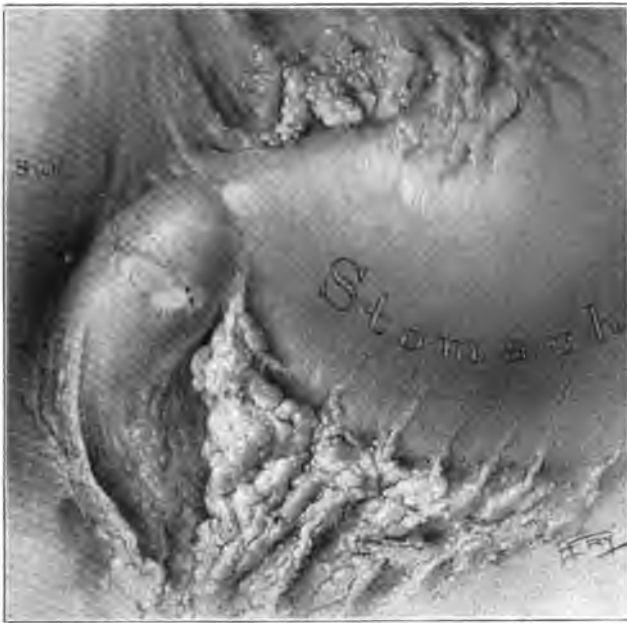


FIG. 38.—Ulcer of the duodenum apparently healed but the cause of recurring hemorrhage. Silk suture which had been placed at a previous operation.

the thickened peritoneal coat will disclose the minute opening which marks the site of chronic perforation. In many cases a probe may be introduced (Fig. 35) through this tract and used as a guide in introducing the cautery (Fig. 36). This observation seems important because it shows the frequency with which this perforation can be demonstrated, and that chronic perforation occurs in practically all chronic ulcers. Knowing from palpation the size of the crater of the

ulcer, the cauterizing is maintained until an opening as large as the crater is made. In this way, as I have pointed out in previous articles<sup>1</sup> any malignant cells within an area of 2 cm. of the cautery point are killed, and the danger of cancer-cell grafting, which is always present in knife excision, is avoided. The opening is subsequently closed with fine chromic catgut, and with reinforcing sutures of silk.

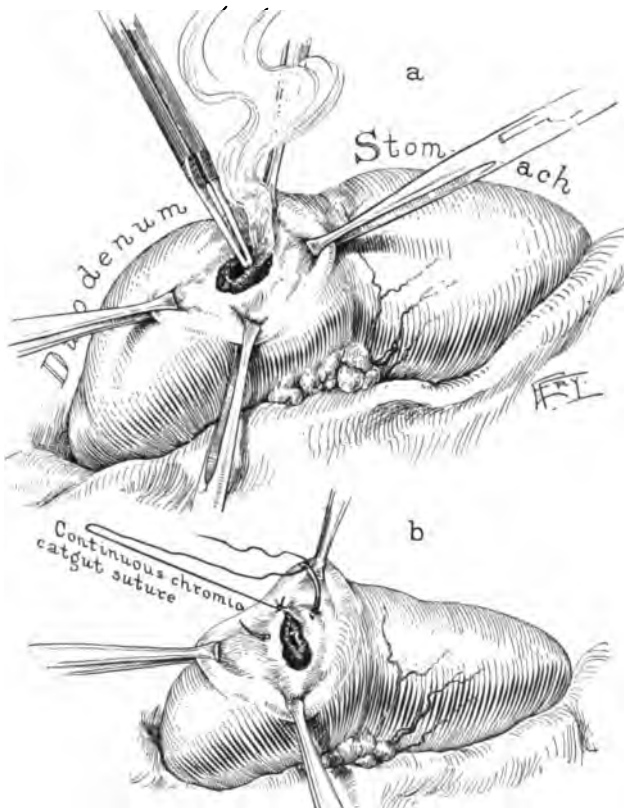


FIG. 39.—a, entire scarred area excised with cautery; b, transverse closure of cauterized opening by first row chromic catgut.

Cauterization is simpler in duodenal than in gastric ulcers, as the duodenal ulcer is usually in direct view and is rarely protected by any surrounding tissue; moreover, the crater of the ulcer is often very small, so that only puncture of the ulcer is required (Fig. 37 a and b). The cautery in duodenal ulcer was first employed in ulcers of the bleeding type, but lately it has seemed advisable to destroy, in this manner,

practically all duodenal ulcers which are readily accessible (Figs. 38, 39 *a* and *b*, and 40).

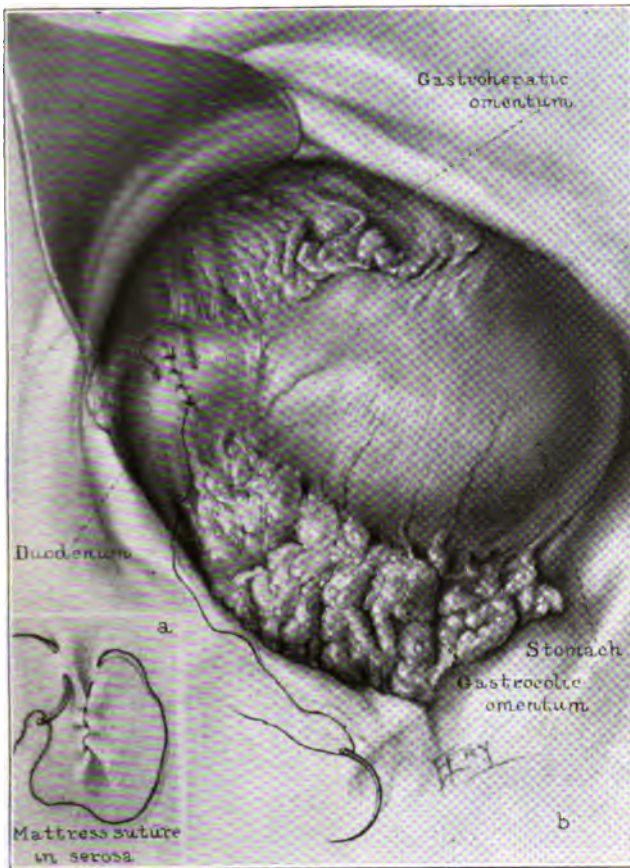


FIG. 40.—*a*, cauterized opening closed by row of catgut; *b*, closure reinforced by a returning second continuous suture.

### SUMMARY

The points which I desire to emphasize are:

1. Hemorrhage following operations for both gastric and duodenal ulcer is of sufficient frequency (2 per cent in duodenal ulcer and 1+ per cent in gastric ulcer) to warrant a revision of operative methods in such cases.

2. Gastro-enterostomy or pyloroplasty alone does not always protect against further hemorrhages, while excision of the ulcer and gastro-enterostomy gives almost total protection.

3. Excision by cautery combined with gastro-enterostomy is the most satisfactory method in the majority of cases of minimizing the possibility of recurrence of hemorrhage in all ulcers which have been associated with hemorrhages, and similar treatment seems advisable in both gastric and duodenal ulcers which have not exhibited such a complication.

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## LIFE EXPECTANCY OF PATIENTS FOLLOWING OPERATIONS FOR GASTRIC AND DUODENAL ULCER\*

D. C. BALFOUR

Efficiency in the surgical treatment of many diseases has been measured in the past by operative mortality, and by the permanency of relief which the patient has secured by operation. With the gradual development of surgical technic, and our increasing knowledge of surgical indications, operative mortality and relief of symptoms have been so favorably influenced that they have now in many fields apparently reached their limit of development. It is also true, however, that in all diseases life expectancy can be said to be the major consideration with the patient, and yet this consideration of pre-eminent interest to the patient has not received the study which it deserves, particularly in those diseases in which operation is conducted primarily for the relief of symptoms.

Diseases of the gastro-intestinal tract stand out most prominently as illustrations of this fact. With the advent of operations such as gastro-enterostomy, in which the normal functioning of the gastro-intestinal tract is changed, the question whether such procedures have influenced the length of life of the given individual becomes one of great importance in connection with the surgical treatment of benign lesions of the stomach and duodenum.

During the several years past we have been repeatedly asked by insurance companies whether a given patient, whom we have operated on for gastric or duodenal ulcer, should be accepted as a good insurance risk. We have had impressions as to the advisability of accepting such risks, but until recently we have never had any actual proof of life expectancy after operations have been carried out on such persons as compared with a group of persons in the general population of similar age and sex.

\* Presented before the American Surgical Association, Atlantic City, June, 1919.  
Reprinted from *Ann. Surg.*, 1919, lxx, 522-525.



As we have always realized the importance of securing positive information along these lines we accepted with readiness the proposal of the Actuarial Society of America that they should study the records at the Mayo Clinic and by their own methods carry out some follow-up investigations with regard to the length of life which may be anticipated in patients operated on for gastric and duodenal ulcer. This Association has recently compiled and published the statistics, and although, in the main, they agree with information which we have been able to secure for ourselves, their methods of investigation, their system of accurate tabulation, and, above all, their unbiased interpretation of such information adds unusual interest and value to the figures which I present.

Unfortunately there is no basis on which the results of the present investigation of operated gastric and duodenal ulcers can be compared with the results in non-operated cases. Not only are no statistics available as to life expectancy in non-operated cases of gastric and duodenal ulcer, but accurate statistics in this group will probably never be entirely possible, because the uncertainties in diagnosis discount more or less the dependability of such figures. On the other hand, surgical statistics are based on proved lesions, and on lesions in which medical treatment has failed. If proved statistics of non-operative cases become available, the surgeon will welcome the opportunity of establishing the fact that the surgical measures of treatment are the most efficient from every standpoint.

The investigation carried out by the Actuarial Society of America was under the direction of Mr. Arthur Hunter, Chief Actuary of the New York Life Insurance Company. It is first interesting to note the success of the methods employed by this society for tracing cases. Of a series of 2431 patients operated on for gastric and duodenal ulcer in the clinic between 1906 and 1915, all but 108 were traced, a percentage record which I am sure has never before been approached.

The figures first show that the operative mortality from all causes\* in 545 cases of gastric ulcers in which operation was done during this period was 4.5 per cent, while in 1684 cases of duodenal ulcer the operative mortality from all causes was 2 per cent. Gastric ulcer carries, therefore, twice the operative risk of duodenal ulcer.

The Association's investigations of the mortality in the years after operation show the following facts:

\* The cause of death has not been considered in this study.

*Gastric ulcer.*—Five hundred twenty-one patients were under observation on the average of three and six-tenth years, and in that time 88 (17 per cent) died from all causes.

*Duodenal ulcer.*—One thousand six hundred fifty-one patients were under observation on the average of three and four-tenth years, and in that time 85 (approximately 5 per cent) died from all causes.

*Gastric and duodenal ulcer.*—Ninety-one patients were under observation on the average of three and eight-tenth years, and in that time 9 (10 per cent) died.

Mr. Hunter's first observations on these statistics are most interesting; I quote verbatim: "The fact that 17 per cent of those operated on for gastric ulcer have died within an average period of observation of three and six-tenth years, and the fact that 5 per cent of those operated on for duodenal ulcer have died within an average period of observation of three and four-tenth years, are in themselves significant. While we cannot tell how many lives have been saved by reason of operation for duodenal ulcer, it may safely be stated that the survival for three and a half years after the operation of 95 per cent is a high tribute to surgery. With such a serious condition as gastric ulcer, a death rate in three and a half years of 17 per cent of those operated on appears to be low. While I cannot prove my statement, I believe that a much larger proportion of persons would have died but for the operation, and that many years of life in the aggregate were saved through surgical treatment."

The chief point of importance in these statistics, however, is gained by comparing the mortality figures of a group of patients subjected to operation for gastric and duodenal ulcer with a group of the general population corresponding in age and sex.

TABLE 1.—GASTRIC ULCER

Deaths in group of 521 persons operated on	
Following Operation	Deaths
First year.....	36
Second year.....	21
Third year.....	11
Fourth year.....	7
Fifth year.....	7
Sixth year and subsequent.....	6
	—
	88

General population group of 521 persons with like distribution as to age and sex observed during the same period of time

Observation	Deaths
First year.....	8.2
Second year.....	6.5
Third year.....	4.9
Fourth year.....	4.1
Fifth year.....	3.0
Sixth year and subsequent.....	5.6
	<hr/> 32.3

It will be noted in Table 1 that the number of deaths in the first year following operation was about four and one-third times the deaths in a like group in the general population; in the second year this number was three and one-fourth times that of the general population, and in the later years it was still less. With an average period of observation, therefore, of only three and one-third years, the number of deaths in the year following operation, when the mortality is highest, has much greater weight in the total than if the observations were conducted for a longer period.

In duodenal ulcer a similar comparison shows most instructive findings.

TABLE 2.—DUODENAL ULCER

Deaths in group of 1651 persons operated on	
Following Operation	Deaths
First year.....	22
Second year.....	20
Third year.....	9
Fourth year.....	10
Fifth year.....	11
Sixth year and subsequent.....	13
	<hr/> 85

General population group of 1651 persons with like distribution as to age and sex, observed during the same period of time

Observation	Deaths
First year.....	24.0
Second year.....	18.6
Third year.....	14.3
Fourth year.....	11.2
Fifth year.....	8.3
Sixth year and subsequent.....	16.7
	<hr/> 93.1

Here we have the rather astounding fact that in the first two years following operation for duodenal ulcer the mortality is only that of the

general population group, and that after the second year the mortality is actually less than in the general population group. These statistics illustrate very strikingly the fact which always has been recognized by surgeons, namely, that gastric ulcer is a much more serious condition than duodenal ulcer, not only from an operative standpoint, but from a standpoint of after-results, and that the patient with a gastric ulcer shows, as a rule, much more evidence of impaired general health than the patient with duodenal ulcer.

### SUMMARY

1. The percentage of operative deaths in the hospital following operation for gastric ulcer was fully twice that following duodenal ulcer, but the percentage in both cases was very low considering the seriousness of the condition.

2. The mortality during the three years following the operation among persons operated on for gastric ulcer was three times as high as that among persons operated on for duodenal ulcer.

3. The mortality among persons operated on for gastric ulcer decreases relatively after operation, but the data are not sufficient to determine the number of years which must elapse before the death rate is similar to that of the general population.

4. The mortality among those operated on for duodenal ulcer in this series was less than that among the general population.

5. The average age at time of operation of those operated on for gastric ulcer was 47 in the case of men, and 43 in the case of women; the average age of those operated on for duodenal ulcer was 44 and 42 respectively.

# A COMPARATIVE STUDY OF THE ANATOMY OF THE SPHINCTER AT THE DUODENAL END OF THE COMMON BILE DUCT WITH SPECIAL REFERENCE TO SPECIES OF ANIMALS WITHOUT A GALLBLADDER\*

F. C. MANN

In previous investigations,<sup>4,5</sup> it was emphasized that the removal of the gallbladder was usually followed by dilatation of all the extra-hepatic ducts. This dilatation did not take place if all the muscle fibers surrounding the common bile duct in its passage through the duodenal wall were destroyed. Furthermore, in our experiments, the sphincter at the end of the common bile duct was either not physiologically active or it was less active than in animals in which the gallbladder had not been removed. Because of these facts great importance is attached to the interrelation of the action of the gallbladder and sphincter. Accordingly, it was believed that an anatomic difference might be found between the sphincter of animals with gallbladders and those without them.

This sphincter has been studied anatomically by Gage, Oddi, and Hendrickson. It has been said that Glisson first suspected such a sphincter, but Gage seems to have been the first to describe the structure. In an extensive study of the ampulla of Vater and pancreatic ducts in the cat, he describes a sphincter around both the common bile duct and pancreatic duct, and another sphincter common to both ducts.

Oddi made an extensive comparative investigation of the sphincter to which his name is usually attached. He studied the duodenal portion of the common bile duct by maceration and histologically in man, the dog, sheep, ox, pig, cat, horse, domestic pigeon, common fowl and guinea fowl. He found that the course of the duct through the duodenal wall differs in the various species of animals. The arrangement of the smooth muscle around the duct likewise differs. In each

\* Reprinted from *Anat. Rec.*, 1920, xviii, 353-460.

species studied, he was able to demonstrate, however, a definite sphincter at the duodenal end of the common bile duct.

A most complete study of the musculature of the entire extra-hepatic biliary system, including that of the sphincter, was made by Hendrickson, in the dog and the rabbit, and in man. Both by maceration and by the microscope he was able to demonstrate a definite sphincter in each species.



FIG. 41.—Photomicrograph of section of hepatic duct of pocket gopher (*F. bursarius*) at about the middle of the course of the duct through the muscularis of the duodenum. The duodenal mucosa is at the top, a lobule of pancreas at the bottom to the right. Note how the muscularis surrounds the duct.  $\times 40$ .

According to the list of species reported by Oddi the gallbladder is absent in only a few, such as the horse and pigeon. In the horse the duct opening is quite patulous, and in the pigeon the duct system is complex. Since it seemed advisable to study the sphincter in other species without a gallbladder, we obtained specimens from four such species, the horse, deer, rat, and pocket gopher (*G. bursarius*); the three latter had not been previously studied. As controls, we also studied the sphincter in the dog, cat, rabbit, guinea pig, ox, goat, pig, sheep, striped gopher (*C. tridecemlineatus*) and mouse, which possess a gallbladder.

The sphincter was studied macroscopically and microscopically; the latter method was found to be the more valuable because many of the specimens were very small. The specimen of the sphincter was secured immediately after the death of the animal and placed in the fixative, usually formalin. The specimen was subsequently trimmed to the smallest size that would give the complete course of the duct, and paraffin serial sections were made.

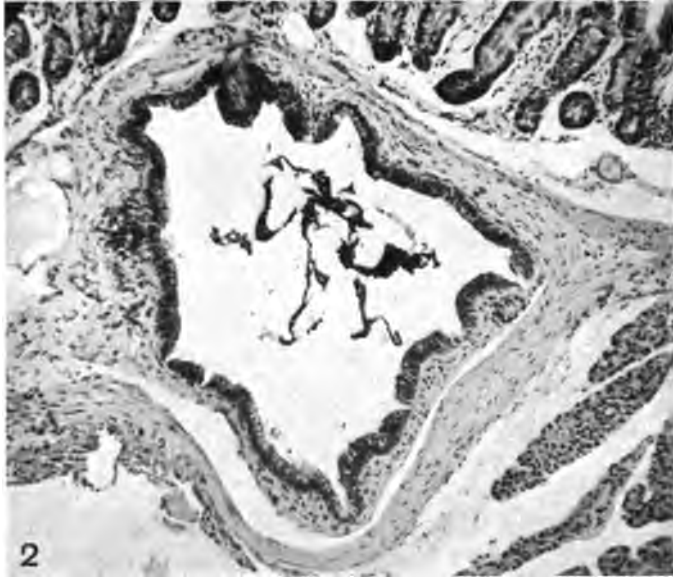


FIG. 42.—Photomicrograph showing a higher magnification of the same section shown in Figure 41. Not only does the muscularis surround the duct but there are a few fibers seemingly passed around the duct and interlacing with the muscle fibers of the muscularis.  $\times 100$ .

This study corroborates the observations of previous investigators with regard to the variability of the course of the duct through the duodenal wall in the various species of animals. In each species the course seems to differ slightly from that of other species. This difference seems to depend mainly on the direction of the duct in relation to the axis of the duodenum and the thickness of the duodenal walls. The relation of the course of the duct to the course of the duodenum was difficult to determine. Angles of various degrees between the course of the duct and the direction of the long axis of the duodenum are noted in various species. In some species the two

are almost parallel for a relatively long distance, but the duct gradually passes through the duodenal wall. In other species the duct seems to pierce the wall of the intestine almost at right angles, but of course it does not actually do so. In a few species the duct turns almost at a right angle to the direction of its course within the duodenal wall. The relative position of the duct to the duodenal wall seems to depend, in a great measure, on the latter. In some species the intramural



FIG. 43.—Photomicrograph of section of hepatic duct of a rat, taken at the point where the duct passes into the submucosa of the duodenum. The duodenal mucosa is at the top, a lobule of pancreas below the muscularis to the left.  $\times 40$ .

portion of the duct is relatively short, particularly in some of the species in which the intestinal wall is thin. In other species the intramural portion of the duct is relatively long. This is due either to a prolongation of the portion of the duct in the muscle-wall, or, as is usually the case, to the extension of the duct in the submucosa for some distance. The opening of the duct through the mucosa also differs in the various species; in most it is no larger than a pen point, but in a few it is patulous. It should be noted that both the direction of the duct through the duodenal wall and the method of opening into the duodenum do not differ in species of animals without a gallbladder, as a group, from species of animals possessing a gallbladder.



The bile duct in each species was found to be surrounded by a bundle of smooth muscle, contraction of which closes the lumen of the duct. The amount of muscle-tissue and the arrangement of it differs considerably in the various species, depending probably on the difference in the thickness of the wall of the duodenum and the course of the duct. In many species it is rather difficult to find muscle fibers which encompass the duct exclusively, because they are so closely



FIG. 44.—Photomicrograph of higher magnification of same section shown in Figure 43. There is a relatively large bundle of muscle which completely surrounds the duct and interlaces with the muscularis of the duodenum. The sphincter is comparably as well developed in the rat as any species studied.  $\times 100$ .

intermingled with the circular fibers of the intestine. As a matter of fact in many specimens the muscle fibers which might act exclusively as a sphincter are very few. Sometimes there is only an accentuation of the muscle coat in the intramural portion of the duct which has extended from the extramural portion. When the arrangement of the circular muscle fibers of the intestine is considered in connection with the fibers which undoubtedly surround the duct, it is justifiable to conclude that a definite sphincter exists in each species studied.

No constant difference was observed in the histology of the sphincter in animals with a gallbladder as compared to those without one, and

no specific anatomic difference was found between the sphincters in the two groups of animals.

### SUMMARY

An anatomic study was made of the sphincter of the duodenal end of the common bile duct in ten species of animals with gallbladders and four species without. Considerable difference was found with regard to the course of the duct through the duoderal wall, and in the arrangement of the muscle fibers around the duct. There is a definite arrangement of muscle fibers which might functionate as a sphincter in each species studied; no difference could be observed in animals that have a gallbladder when compared with those without one. There is no doubt that anatomically some species of animals lacking a gallbladder have an arrangement of muscle around the duodenal end of the bile duct which can act as a sphincter.

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# A STUDY OF THE TONICITY OF THE SPHINCTER AT THE DUODENAL END OF THE COMMON BILE DUCT\*

With Special Reference to Animals without a Gallbladder

F. C. MANN

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Previous work on the function of the gallbladder has shown that cholecystectomy is usually followed by dilatation of all the extrahepatic ducts. This dilatation is dependent on an intact sphincter at the end of the common bile duct. This would seem to imply that there is some relation between the action of the sphincter and that of the gallbladder, a possibility which has been used by Oddi and Meltzer in explaining the cause of some of the diseases of the biliary tract. In a study of the anatomy of the sphincter, no difference was found in species of animals with a gallbladder as compared with those without one.<sup>3</sup> A comparable study of its physiology was therefore made.

The physiologic action of the sphincter at the duodenal end of the common bile duct has been studied, although only in the dog and the cat, by Oddi, Archibald, and Rost; only the two former investigators measured the tone of the sphincter. Oddi found that the sphincter in the dog withstood a pressure of about 50 mm. of mercury or an equivalent of 675 mm. of water. Archibald found that the sphincter in this same species withstood a pressure as high as 600 mm. of water. Both investigators found that mechanical or chemical irritation throws the sphincter into a spasm.

A series of observations on the physiologic action of the sphincter has been made in our laboratory; a complete report will be made later. The present article deals only with a comparison of the tone of the sphincter in species with a gallbladder and in those without one. We had access for this research to only two species in which

\* Reprinted from Jour. Lab. and Clin. Med., 1919, v, 107-110.

the gallbladder was lacking, the rat and pocket gopher (*G. bursarius*).<sup>\*</sup> For controls the dog, cat, goat, rabbit, striped gopher (*C. tridecemlineatus*), and guinea pig were used.

The method of estimating the tone of the sphincter was simple. The animal was lightly etherized; in a few experiments urethan was used, a cannula was carefully placed in the common bile duct (in the species without a gallbladder in the hepatic duct), as far as practicable from the duodenum, with its point directed toward the duodenum. A T-tube was attached to the cannula and one arm of the tube was arranged so that it could be connected to a syringe; the other arm was connected to a straight glass tube. This T-tube was about 50 cm. in length and had an internal bore of approximately 2.5 cm. The glass tube was graduated in millimeters. Great care was taken to keep the duodenum protected during the operative procedures.

The tone of the sphincter was estimated by two methods: First, an aqueous eosin solution was passed slowly and cautiously into the tube until the point at which it began to flow into the intestine was reached. The findings were recorded. Second, the solution was passed quickly into the tube to a high pressure and the point noted at which it ceased to flow into the intestine. In both instances the length of the column of water, after the fluid became stationary, was taken as a measure, expressed in millimeters, of the tone of the sphincter. The specific gravity of the eosin solution was but slightly greater than that of distilled water and, since the study was a comparative one, this difference was ignored. The solution was either at body or room temperature. Care was taken to have the system free from air before beginning observations. It is obvious that this method does not give absolutely the correct measure of the tone of the sphincter as there are many complicating factors and sources of error. The major portion of the errors may be attributed to two causes: First, the pressure taken as the measure of the duct might be due to other factors, such as friction, and so forth, making the reading greater than it should be. Second, the anesthetic and operative manipulation might decrease the muscle tone, tending to make the measured pressure less than the pressure of the duct really was. As a matter of fact both of these factors were found to be sources of error, but they were in the main obviated so that an approximate reading could be made.

<sup>\*</sup> These experiments were completed in 1917, but publication was delayed because of attempts to obtain data from a larger number of species lacking a gallbladder. The pigeon and horse were used, but technical difficulties caused failure.

The amount that the reading was complicated by resistance to outflow other than that produced by the tone of the sphincter was determined by taking another reading after deep etherization, bleeding, and formalin injections into the duct and after the death of the animal. It was thus determined that the residual pressure was practically a measure of the tone of the sphincter in large ducts, as in the dog and goat; in the smaller animals, a correction of 10 per cent might occasionally have to be made. The part the anesthetic played in complicating the experiment was studied by using ether, urethan, and, in the case of the dog, the development of a method of studying the action of the sphincter in an unanesthetized animal. From the results of the control methods it seemed that the anesthetic as administered did not offer a very great source of error. The operative manipulations also produced changes, either an increase or a decrease in the tone of the sphincter. Peristalsis was also considered, because peristaltic waves affect the outflow from the common bile duct.

The pressure which seemed to measure the tone of the sphincter was found to vary considerably in the different species and different individual animals. However, the sphincter in each species of animal possessing a gallbladder, except the guinea pig, withstood a minimum pressure of 100 mm. water; sometimes the pressure was much greater, very rarely it was less. In the guinea pig, the pressure withstood was rarely more than 75 mm. and frequently considerably lower; this seemed to be due to the fact that as the common bile duct is very short in this species, the trauma incident to the insertion of the cannula was great. In a very few animals of other species the sphincter did not seem to have any tone.

The pocket gopher and rat were the only suitable species without a gallbladder obtainable for investigation of the tone of the sphincter. The results of a large number of experiments are the same; in no instance was any pressure, or at the most only a very slight pressure, usually not more than 30 mm., maintained by the sphincter. In most cases, all the fluid passed into the duodenum, leaving only a very slight residual pressure.

As I have stated, it was very difficult because of many complicating errors to evaluate the results in this investigation. In the dog and cat, which had been studied by previous investigators, our results did not show that the sphincter withstood so great a pressure as that recorded by others. On the other hand, some evidence of a sphincteric

tone was found in each species with a gallbladder. Even in the guinea pig there was definite evidence of this action. No such evidence was obtained in the two animals lacking a gallbladder, the rat and the pocket gopher, although many experiments were performed. When the mass of data from a large series of experiments is considered, this distinction between the two groups of species becomes very clear.

### SUMMARY

The tone of the sphincter at the duodenal end of the common bile duct was studied in species of animals possessing a gallbladder and in two species in which the gallbladder is lacking. It was found that the tone of the sphincter under the experimental conditions studied varied considerably in the different animals and various species. In each species possessing a gallbladder, however, the sphincter was usually able to withstand a minimum pressure of from 75 to 100 mm. water. In the species lacking a gallbladder, the sphincter would not withstand pressure, or only pressures of less than 30 mm. water. While anatomic studies have shown that a sphincter is present in each species lacking a gallbladder, the sphincter does not seem to functionate appreciably.

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## EARLY LESIONS IN THE GALLBLADDER\*

W. C. MACCARTY AND J. R. CORKERY

The study of early pathologic conditions in the gallbladder has been greatly facilitated by cholecystectomy, an operation which many surgeons have deemed advisable in preference to cholecystostomy. In their experience, many patients in whom the organ had been drained returned to them with symptoms unrelieved. The desired relief in such cases seems to have been accomplished, at least in a much higher

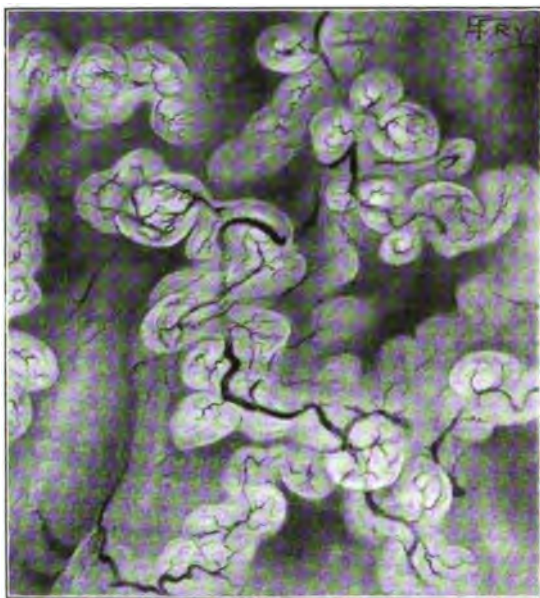


FIG. 45.—Villi of a gallbladder in an early stage of congestion and edema.

percentage, by the secondary complete removal of the organ. This experience with such cases following a secondary cholecystectomy has led, in the last five years, to the custom of primary cholecystectomy in preference to cholecystostomy in patients with a visible lesion and also in some patients in whom there is no visible gross pathology but a

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definite clinical picture pointing to this organ, plus enlargement of lymphatic glands along the ducts.

From Jan. 1, 1913 to Jan. 1, 1919, 4,998 gallbladders were removed at the Mayo Clinic. Of these, 4,824 (96.5 per cent) showed unquestioned gross pathologic lesions (Table 1).

In this series of conditions it may be seen that there were 157 with slight lesions and 17 grossly "normal," most of which showed definite changes in the villi on examination with a high power dissecting microscope or in microscopic sections.

TABLE 1.—CLASSIFICATION OF 4,998 GALLBLADDERS

	Specimens
1. Cholecystitis catarrhalis acuta.....	17
Cholecystitis catarrhalis acuta (with "strawberry" appearance).....	9
2. Cholecystitis catarrhalis subacuta.....	112
Cholecystitis catarrhalis chronica.....	2,021
3. Cholecystitis catarrhalis chronica (with "strawberry" appearance).....	948
Cholecystitis catarrhalis chronica (with adenoma in the wall).....	1
Cholecystitis catarrhalis chronica (with accessory fundus).....	1
Cholecystitis catarrhalis chronica (with diverticula).....	4
Cholecystitis catarrhalis chronica (with old perforation).....	1
Cholecystitis catarrhalis chronica (with very slight lesion).....	38
Cholecystitis catarrhalis chronica (?).....	157 (3.1 per cent)
4. Cholecystitis catarrhalis papillomatosa.....	212
Cholecystitis catarrhalis papillomatosa (with "strawberry" appearance).....	129
Cholecystitis catarrhalis papillomatosa (with "strawberry" and cystic appearance).....	1
Cholecystitis catarrhalis papillomatosa (with a diverticulum).....	1
Cholecystitis catarrhalis papillomatosa (subacuta).....	1
Cholecystitis catarrhalis papillomatosa (malignum).....	1
Cholecystitis catarrhalis papillomatosa (malignum (?).....	1
5. Cholecystitis catarrhalis (carcinomatosa).....	22
Cholecystitis catarrhalis carcinomatosa (?).....	1
6. Cholecystitis chronica.....	900
Cholecystitis chronica (with honeycomb appearance).....	8
Cholecystitis chronica (with perforation of wall).....	1
Cholecystitis chronica (with calcification of wall).....	1
7. Cholecystitis chronica cystica.....	112
Cholecystitis chronica cystica (empyema).....	24
8. Cholecystitis acuta.....	81
Cholecystitis acuta (with perforation of wall).....	1
9. Cholecystitis purulenta necrotica.....	168
Cholecystitis purulenta necrotica (with "strawberry" appearance).....	5
10. Cholecystitis ulcerosa.....	1
11. Cholecystitis epitheliomatosa (with gall stones).....	1
12. "Normal" gallbladders (gross diagnosis).....	17 (0.34 per cent)





FIG. 46.—Villi of a gallbladder showing congestion and distortion in early cholecystitis.

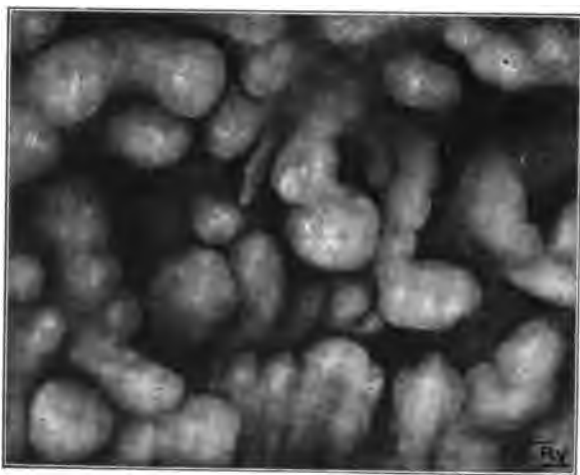


FIG. 47.—Edematous villi having a bulbous appearance and showing pale areas which are due to deposits of a lipoid substance in the epithelium or just beneath the epithelium in the connective tissue stroma.

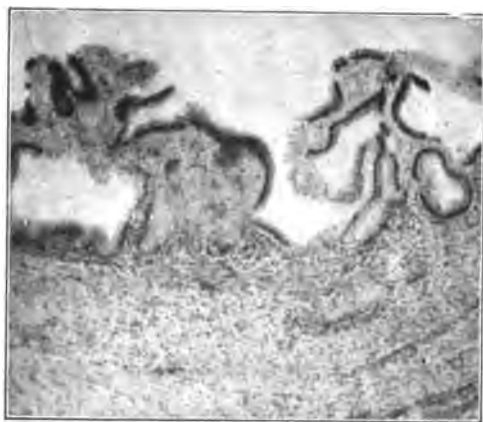


FIG. 48.—Villi in an edematous condition.

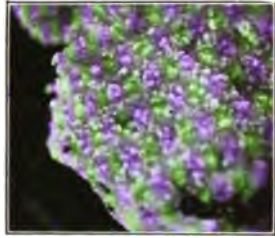


FIG. 49.—A condition of edema of the villi associated with deposits of lipid material in the epithelium and stroma.

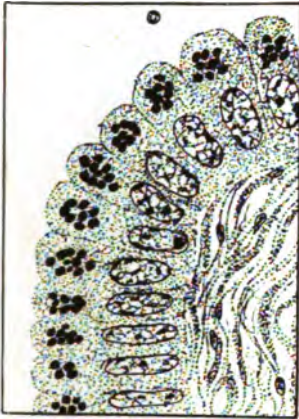


FIG. 50.—Diagrammatic sketch showing the location of lipid substance in the epithelium. Made from a section stained with scarlet R.

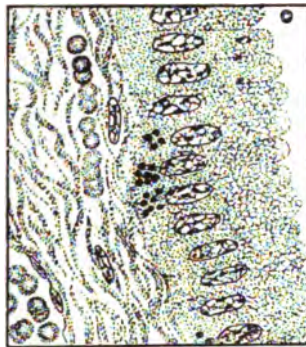


FIG. 51.—Diagrammatic sketch showing the location of the lipid substance in the cells but near the stroma.

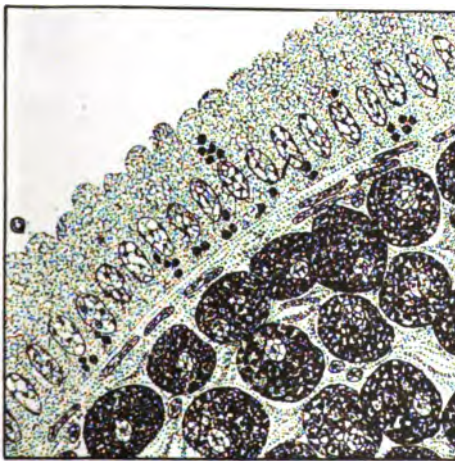


FIG. 52.—Diagrammatic sketch showing the lipid substance in the epithelium and in the cells of the stroma.

The early changes in the gallbladder consist of:

1. Congestion and edema of the villi frequently associated with a bulbous appearance (Figs. 45, 46, 47, and 48), which, on casual gross examination make the villi appear cystic. Occasionally they are cystic.

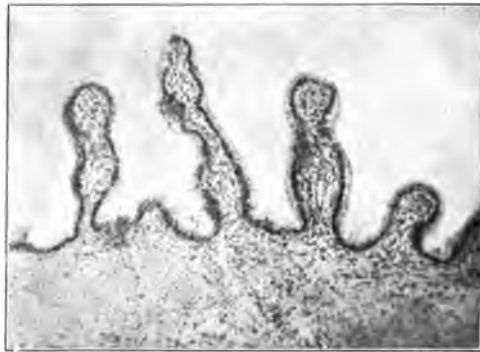


FIG. 53.—Section through the mucosa of a gallbladder in a mild condition of chronic catarrhal cholecystitis. The villi contain many lymphocytes.

The mucosa in advanced stages of this congestion and edema sometimes presents the appearance of being covered with small fish scales (Fig. 49), an appearance which is due to the presence of a lipid infiltration in the stroma or epithelial cells (Figs. 50, 51, and 52).



FIG. 54.—Section through the mucosa of a gallbladder showing lymphocytic infiltration of the villi and the underlying stroma.

2. Local or general slight degree of lymphocytic infiltration which manifests itself only in a slight enlargement of the villi (Figs. 53 and 54) and a cloudy or duller appearance.

3. Local or general slight degree of lymphocytic infiltration is

seen in the mucosa alone, which might possibly be considered normal since the mucosa probably contains a certain number of lymphocytes

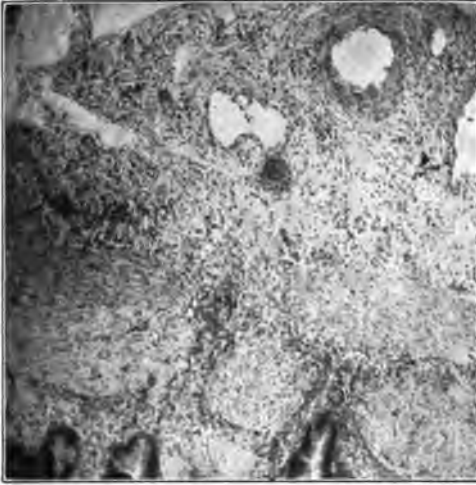


FIG. 55.—Section of the submucosa of a gallbladder, showing lymphocytic infiltration and fibrosis.

but when seen in association with a lymphocytic infiltration in the submucosa, muscularis, and subserosa (Fig. 55) very probably indicates a



FIG. 56.—Section through the mucosa of a gallbladder showing lymphocytic infiltration and fibrosis in the villi. There is a glandular increase and the villi have lost their tentacular appearance.

pathologic condition. Such infiltration is associated with a bulbous appearance of the villi or a thickening of the bases of the villi (Figs. 56 and 57).

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4. The presence of fibrosis (Fig. 57) in the villi which usually are not thin and tentacular (in sections) like those of the perfectly normal organ. The fibrosis sometimes extends into the submucosa, muscularis, and subserosa (Fig. 55).

5. The presence of lymphocytic infiltration and fibrosis, such as described above, plus the presence of a finely granular or lipid substance in the epithelium (Figs. 50 and 51) or just below the epithelium in the mucosa (Fig. 52).

6. The presence of slight or no lymphocytic infiltration and fibrosis plus the presence of large spheroidal cells filled with finely granular lipid substance in the mucosa and sometimes in the submucosa (Fig.

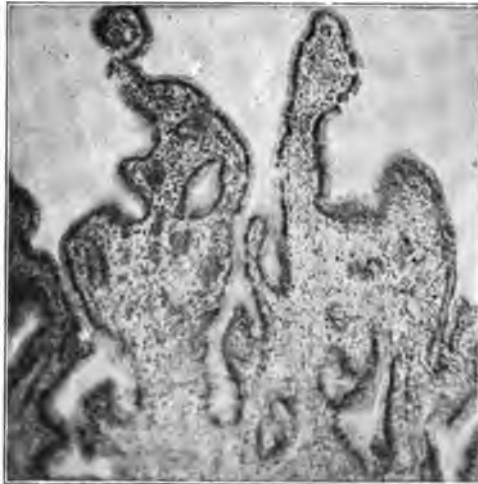


FIG. 57.—Section through the mucosa of a gallbladder showing lymphocytic infiltration, fibrosis, and distortion of the villi.

52). These cells are similar to those which have been described in the so-called “strawberry” gallbladder<sup>2, 3</sup> and in papillomas.<sup>1</sup> This substance may not be visible grossly but may sometimes be detected with the high power dissecting microscope (Fig. 47). It is the substance which gives villi in the “strawberry” gallbladder and papillomas their yellow or white appearance.

The conditions which have been described above do not alter the gross exterior of the organ, nor do they alter greatly the internal appearance to the naked eye.

It is this group of slight pathologic reactions which has made many

surgeons, who believe that a cholecystectomy is the operation of choice in cholecystitis, somewhat slow in carrying out their belief in practice. Also, it is probably this group which is so frequently seen in association with stones and has led many observers to believe that stones occur in perfectly normal gallbladders.

With our present knowledge we are not prepared to say definitely that such early conditions alone present sufficient symptoms to make a definite clinical syndrome, especially in view of the fact that recent studies made by one of us (MacCarty) indicate that such conditions in the gallbladder are also associated with somewhat similar changes in the extrahepatic and intrahepatic bile ducts, which might readily interfere with hepatic function and, therefore, produce clinical disturbances. As a matter of fact, such patients do present some general disturbances which clinicians refer to under the broad heading of toxemia.

This paper has for its object the stimulation of greater interest and more detailed research in conditions of the bile passages which have heretofore been mistaken for normal.

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## JAUNDICE AND ITS SURGICAL SIGNIFICANCE\*

C. H. MAYO

Jaundice as a symptom of disease may present a very serious problem in tracing its cause. In approximately 50 per cent of the cases seen the absorption of the bile is due to obstruction of the common duct by gallstone; in 20 per cent of all cases it is due to absorption of bile in the liver, or infective or catarrhal jaundice without duct obstruction. Most of the latter cases occur in children and young persons, just enough occurring in middle age and later to make a differential diagnosis necessary, as attacks of pain sometimes accompany this infectious disease or the patients actually have gallbladder disease.

It is not my intention to discuss the diagnosis of the various causes of jaundice, but to consider the treatment of obstructive jaundice in cases in which the patient is on the table, the abdomen is open, and jaundice is either present, or the patient is having a free interval between recurring attacks. The surgeon must have in mind the fact that jaundice is an essential feature of several conditions, and that it is an indication of serious disease in the majority of cases. The idea that jaundice may be a symptom in fairly normal persons over long periods evidently came about from the observation of hemolytic acholuric jaundice caused by splenomegaly, a surgically curable disease, sometimes complicated with gallbladder disease and stones. From 5 to 8 per cent of cases of jaundice are due to serious infection of the gallbladder, possibly gangrene, with or without stones; they are usually accompanied by a degree of pancreatitis with marked swelling of the lymph glands on the three ducts; all persons have one on each duct but no one more than two. The liver is congested and dark; the ducts are slightly enlarged and contain much flocculent material which is also found in the gallbladder in which stones are usually present.

Jaundice from cancer presents a very serious problem, although it represents but 15 per cent of the cases seen; one-half of these are from cancer of the liver, the other half from cancer of the pancreas,

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or the gallbladder and ducts. Patients with cancer of the pancreas or in the ampulla of Vater may be relieved, often for many months by short-circuiting the obstructed area. We have not had a permanent cure from transduodenal extirpation of tumor of the ampulla; and it must be admitted also that it is sometimes difficult positively to determine whether the hardening of the pancreas causing obstructive jaundice is of a malignant or of an inflammatory nature. Jaundice from cirrhosis, with ascites usually present, occurs in about 8 per cent of cases. The old classification made by Courvoisier still remains a true observation, in which in about 84 per cent of the cases of stone in the common duct the gallbladder was shrunken or atrophied while in 92 of 100 cases of obstruction due to lesions in the ampulla or pancreas or other conditions, the gallbladder was dilated or enlarged; in the remaining 8 cases it was either normal or atrophic.

In cases of chronic jaundice with obstruction the distended gallbladder and ducts are often filled with a clear mucoid fluid indicating, I believe, that the power of the mucous gland to secrete the less absorbable mucus which fills the ducts is greater than the power of the liver to secrete bile, and forces the liver with its lower blood pressure to absorb the bile. In cases of late operation at which the so-called white bile is found, failure of the power of biliary excretion to appear within a day or two following the operative drainage is a most unfavorable symptom. Long continued jaundice slows the coagulation time of blood; as a rule if the coagulation time is under ten minutes it is not of serious moment, but a ten to twenty-five minute period is not uncommon, and in some cases the blood will not coagulate in an hour. Patients in whom the blood leaves the vessels as shown by numerous subcutaneous hemorrhages should be medical cases until improvement occurs before surgery is indicated. Calcium has been given, with questionable relief, to reduce the delayed coagulation time of patients with chronic jaundice who are being prepared for operation. The best measure in cases with twelve minutes or more coagulation time is the transfusion of acceptable human blood. Patients whose coagulation time is greatly reduced are given one transfusion and the blood is tested the next day. If improvement is marked operation is performed, but if improvement is slight transfusion is repeated just preceding the operation, and, if there is hemorrhage during the next few days, transfusion is again repeated with occasional benefit.

If the gallbladder shows marked evidence of disease, especially



in cases of stone in the common duct, a cholecystectomy is performed. After removal of the gallbladder the cystic duct is split through into the common duct to permit of an exploration; here the pliable metal spoons and bulb-tipped probes and the Gusse fenestrated stone forceps of various sizes are useful. In the rare instances in which the gallbladder has already been removed a more favorable location than the cystic duct area can be selected. In more severe infection with degrees of gangrene the gallbladder should be removed unless the serious condition of the patient makes haste imperative; then it is drained with or without drainage of the common duct, depending on whether or not bile flows from the gallbladder.

In such cases the gallbladder is split on each side with scissors from top to bottom one quarter of an inch from its attachment to the liver. The free flap is turned downward, exposing the obstructing stone in the cystic duct; the duct is clamped in forceps and divided. The mucous membrane remaining on the liver attachment readily peels off, leaving the outer layer of the gallbladder for protection since if this should be peeled off serious hemorrhages, difficult to control may result. Suturing such a liver adds to the infective condition for the liver structure does not permit of drawing sutures sufficiently tight to check serious hemorrhage from its surface; this is one of the reasons why cholecystostomy has been made in some cases. A knowledge of the size of the various ducts is quite essential; in a healthy person the lumen of the cystic duct is about one-eighth of an inch and the lumen of the common duct about one-sixth of an inch. When it is only a little enlarged and with jaundice present infection is the essential factor. A gallbladder which has been rendered functionless by nature, disease, or operation causes dilatation above the normal of the common and hepatic ducts. A serious and not uncommon cause of jaundice is the too radical extirpation of the gallbladder and cystic duct and section of the common duct in cases in which jaundice was not a previous symptom, and in which the hepatic duct is mistakenly ligated for the cystic; primary jaundice and later a prolonged biliary fistula result, following which intermittent closure leads to intermittent jaundice. In such cases if the condition is not recognized immediately and very early union effected by means of a Sullivan T-tube the common duct undergoes atrophy and cannot be utilized again. The effort to secure delivery of bile from direct incision of the liver or by trocar, tapping a dilated duct, is a last resort from which relief is only.

temporary, and if unsuccessful life is possibly shortened by free hemorrhage.

Jaundice in which the head of the pancreas shows marked hardness, lobulation, and increase in size, requires most careful consideration. If the gallbladder is distended the condition is due either to pancreatitis or to a malignant change, since the pancreas, as Opie has shown surrounds the common duct in 32 per cent of persons sufficiently to make obstruction possible by pressure. Obstruction from swelling at the tip of the ampulla may cause a pancreatitis by forcing bile through the major duct of Wirsung back into the pancreas and out of the duct of Santorini. The pancreas, in its development, is evidently prepared for such emergencies since all the ducts of the organ open into the lumen of the larger ducts by passing along its wall for some distance. The closure of the ducts is caused by tension, which is nature's method of protecting all important ducts, such as the salivary and common ducts, and the ureters near their exits, as was shown by Coffey.

A careful examination of the pancreas in all cases of gallbladder disease or surgical gastric disease indicates that the pancreas is secondarily involved by infection following gallbladder disease more frequently than has been supposed. When secondary infection of the pancreas is a marked feature of gallbladder disease it may be advisable to provide drainage from the common duct, but usually the gallbladder may be looked on as a primary focus, and should be removed. In most of the simple obstructions due to stones in the common duct effective drainage is established after removal of the stones by means of the Robson tube passed into the opening of the common duct and up into the hepatic duct. The tube is held by a fine catgut suture as it emerges through the common duct incision. The suture serves also to close the opening about the drain. In cases of obstruction associated with distention of the gallbladder short-circuiting is best done by attaching the gallbladder, after it has been emptied, to the duodenum. An opening one-half inch in diameter is made in the fundus of the gallbladder, the peritoneum is denuded for about one-quarter of an inch from the opening; it is then passed for one-quarter of an inch, through an incision at a conveniently near point, into the lumen of the duodenum. Such openings prove more permanent than the margin-to-margin union of the opening in the gallbladder to the opening in the duodenum. In some cases with elongated cystic duct the

gallbladder is removed down to its pelvis and this is passed through an opening in the duodenum which is then sutured around the cystic duct (Fig. 58).

Probably the most desperate and difficult cases of jaundice to deal with are those which follow extirpation of the gallbladder and unintentional division of the common duct. The distended hepatic duct is searched for, usually among the adhesions of from two to four previous

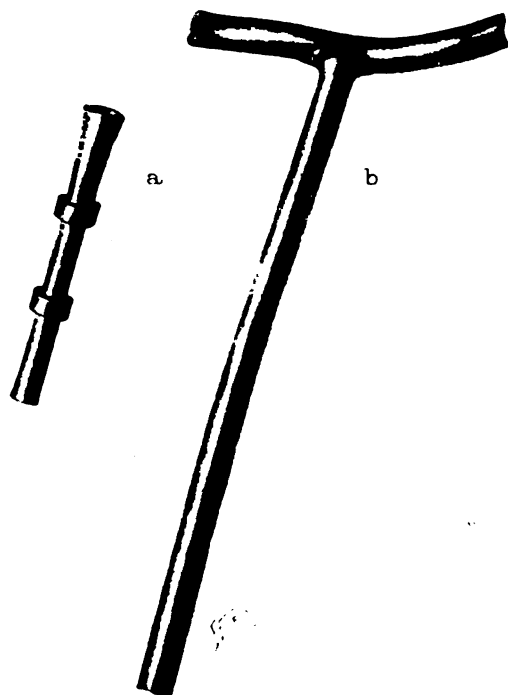


FIG. 58.—(a) Sullivan tube for common duct drain; (b) buried tube (C. H. Mayo) for uniting hepatic duct to stomach or duodenum.

operations, or the temporary discharging fistula leading to the hepatic duct is followed. In cases in which the end of the hepatic duct is found opposite the duodenum or opposite the pyloric ring the pylorus and duodenum are also mobilized and the union is made to the duodenum; this is the preferable method. Often the prepyloric region of the stomach is found adherent beside the opening of the duct. In such cases it is best to disturb the adhesions as little as possible and

to anastomose the hepatic duct to the prepyloric portion of the stomach. To maintain this opening until nature contracts the tissues, developing firm union and a mucous-lined tube, it is only necessary to unite the end of the duct to the mucosa of the stomach or bowel (Fig. 59).

To facilitate this I have devised a drain which has proved most efficient and is made by cutting off the bell end of an ordinary male catheter, slipping two small rings cut from the next larger sized cathe-

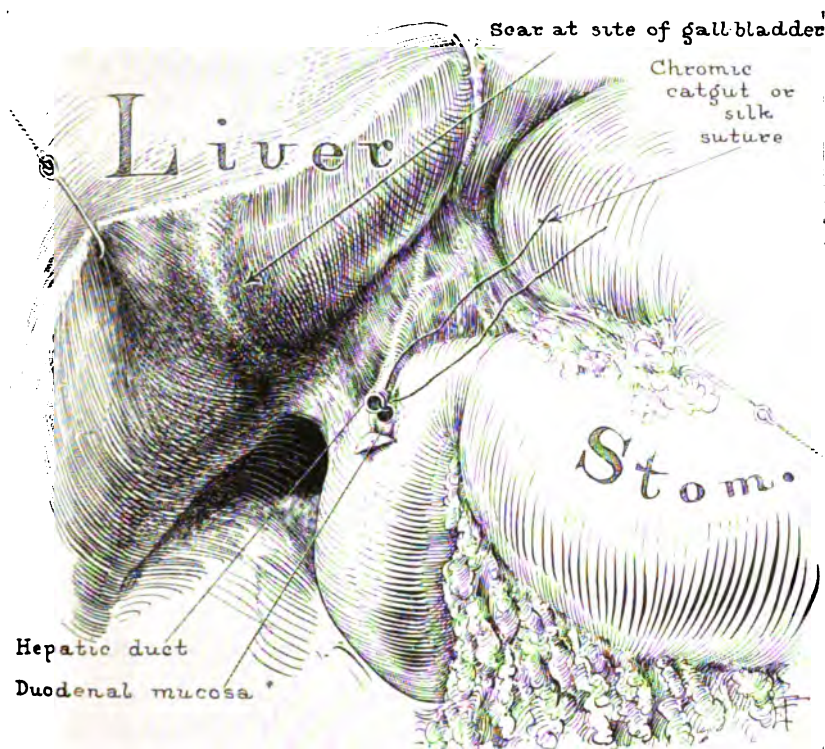


FIG. 59.—Preparation for anastomosis of hepatic duct and duodenum.

ter over the smaller part of the tube, and gluing these rings with rubber cement. This little drain, varying in length from one and one-half to two and one-fourth inches, is passed bell end upward into the hepatic duct, which has been loosened for a short distance. The catheter drain is sutured to the end of the hepatic duct and an opening is made into the bowel or stomach through which the lower end of the drain is passed, the lower ring catching in the wall of the bowel or stomach and the second ring just inside the end of the hepatic duct; the outer wall

of the stomach or bowel is sutured around the end of the hepatic duct and protected by gastrohepatic or gastrocolic omentum adjusted around the anastomosis by sutures. The rings on the tube may hold it in place for as long as several months, or until the contraction has relaxed and the mucous membrane of the duct is united to the lumen of the bowel or stomach. In cases in which this union to the stomach is made all the bile passes into the stomach, but this is of no serious consequence and does not give any distressing symptoms (Fig. 60).

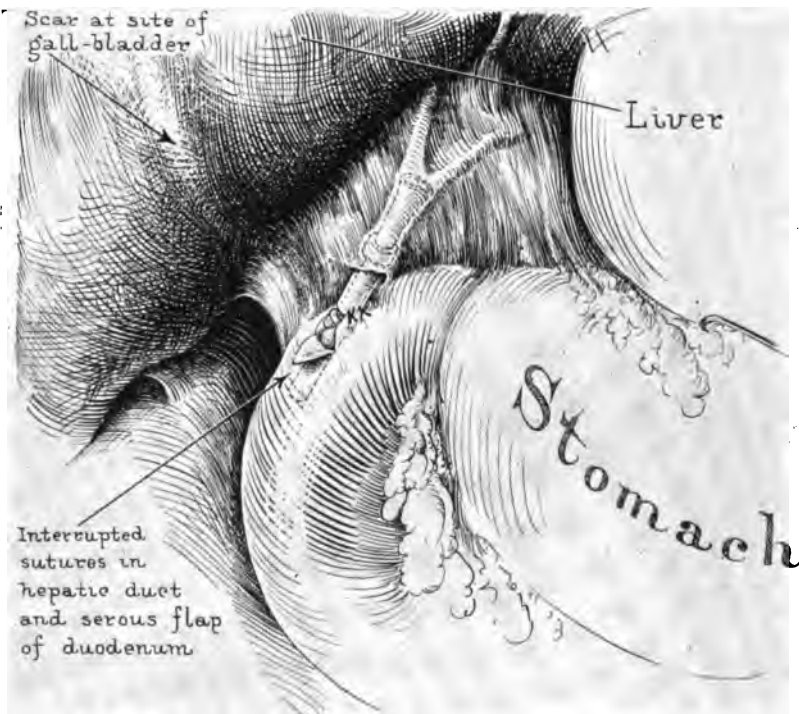


FIG. 60.—Suturing partially completed; tube in place.

During the years 1916, 1917, and 1918 in 13 cases seen it was necessary to unite the hepatic duct either to the duodenum or to the stomach; two of the patients died. Jaundice is a late symptom of gallstone, in the majority of cases the result of neglect to recognize the condition or to advise operation in the preventive period. The mortality following cholecystectomy in the treatment of cholecystitis with or without stones is low, only 1.8 per cent in 2,460 operations performed during the period of three years. There were 337 cases in which

cholecystectomy and choledochotomy were both done, with a mortality of 3.2 per cent. In a group of 36 cases of very serious obstruction and malignancy cholecystostomy and choledochotomy were done with a mortality of 16.6 per cent. Choledochotomy alone was done in a somewhat similar group of 47 cases, with a mortality of 15 per cent. If all the choledochotomies are grouped together, however, the mortality in the 420 cases is but 5.7 per cent, too high a mortality for simple cases of stone and obstruction, and too low for the late and complicated cases, including the cancers. Stones were found in the common duct in 274 of the 420 cases.,

# THE HISTOGENESIS OF CARCINOMA IN THE ISLETS OF THE PANCREAS\*

E. J. HORGAN

The earliest stages of carcinoma have been found in association with chronic inflammatory changes in many organs of the body; therefore it seemed theoretically possible that similar neoplastic changes might be found in association with chronic pancreatitis. With this idea in mind I examined 262 pancreases which were removed at necropsy from patients who died with ulcer of the stomach, ulcer of the duodenum, cholecystitis with and without stones, cholangitis with and without stones, and carcinoma of the stomach, liver, gallbladder, and bile ducts. In no case in this series was a definite advanced carcinoma of the pancreas studied, although comparison was made of thirty-six specimens of tissue from late carcinoma with the tissue showing early changes.

In the cases available for study the pathologic conditions of the pancreas found in association with those chronic upper abdominal lesions mentioned were acute and chronic pancreatitis, stages of fat necrosis, simple cysts, cyst adenomas, papillary cystadenomas, hypertrophy and hyperplasia in the islets of Langerhans. Of these conditions, hypertrophy and hyperplasia in the islets in chronic pancreatitis were selected as the object of this special investigation. In order to obtain more accurate knowledge which might throw light on the histogenesis of carcinoma of the pancreas, a detailed study of pathologic specimens, grossly and microscopically, was made. This was supplemented by the study of the normal development and structure of the pancreas.

## EMBRYOLOGY

The pancreas in man develops from two anlagen which appear in the embryo of 3 to 4 mm. in length. The dorsal pancreatic anlage begins as an outpouching on the duodenum, the ventral pancreatic anlage as a grooved bud arising from the common bile

\* Reprinted from Jour. Lab. and Clin. Med., 1920, v, 429-442.

duct (Fig. 61). The growth of the dorsal pancreas is more rapid than that of the ventral. The anlagen grow separately until they meet

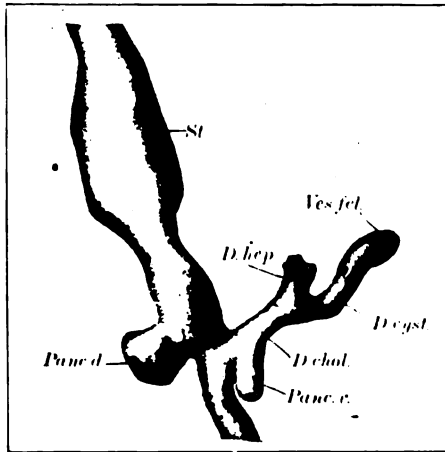


FIG. 61.—Photograph from Thyng. "Reconstruction from a human embryo at 7.5 mm. (H. E. C. 256).  $\times 55$  diams. *D. chol.*, ductus choledochus. *D. cyst.*, ductus cysticus. *D. hep.*, ductus hepaticus. *Panc. d.*, pancreas dorsale. *Panc. v.*, pancreas ventrale. *St.*, stomach. *Ves. fel.*, vesical fellea."



FIG. 62.—(H. 187 Univ. of Minn. Collection.) Microphotograph of pancreas in embryo (158 mm. C. R. length) showing relation to stomach and left adrenal.

posterior to the duodenum where they coalesce and continue development in one mass in the dorsal mesentery. The body and tail grow upward and to the left lie in the dorsal mesogastrium posterior to



the stomach. As the stomach and dorsal mesogastrium change position the pancreas moves within the dorsal mesogastrium until its position is transverse when it becomes firmly fixed to the parietal peritoneum of the posterior abdominal wall. In one embryo,\* 26 mm., which I studied the dorsal and ventral anlagen are fused.

The primitive outpouchings are lined with a columnar epithelium similar to that in the duodenum. As the buds grow the epithelium develops branching ducts ramifying the connective tissue. The main duct of the dorsal pancreas opens into the duodenum while the main duct of the ventral pancreas opens into the common bile duct at the ampulla. When the dorsal and ventral anlagen unite the main duct

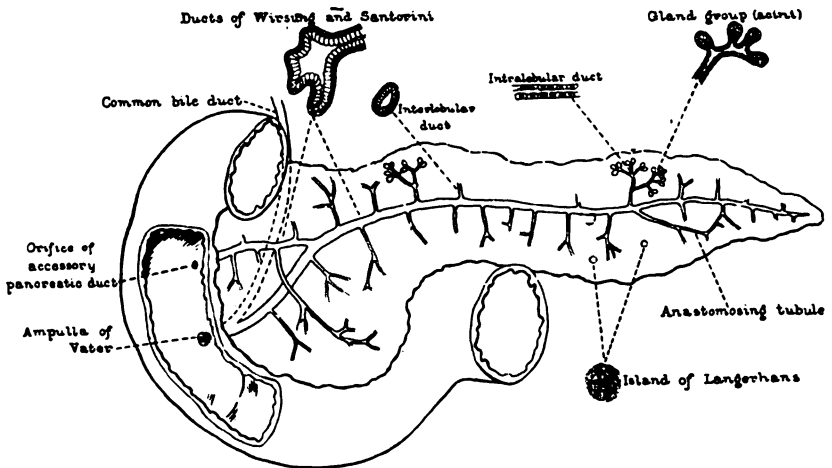


FIG. 63.—Diagram of pancreas showing its histologic units.

of the ventral pancreas makes a lateral anastomosis into the main duct of the dorsal pancreas. In this way the main duct of the ventral pancreas with the distal half of the duct of the dorsal pancreas forms the duct of Wirsung, and the proximal half of the duct of the dorsal pancreas is the duct of Santorini. When the embryo is from 26 mm. to 33 mm. in length, and the tail of the pancreas extends well out into the dorsal mesogastrium, branching tubules can be seen throughout the gland. No acini nor islets are to be seen at this stage and there is no evidence of lobulations. The connective tissue forms the major portion of the organ. At the end of the branches of the main duct the tubules have an enlarged bud. This bud branches and forms new

\* University of Minnesota Collections No. H 29.

tubules until the acini begin to form by several buds at the tip of each tubule. After the acini have begun to form throughout the gland the

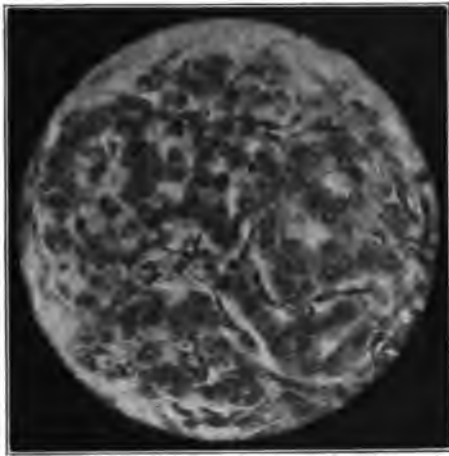


FIG. 64.—(H.187 Univ. of Minn. Collection.) Microphotograph of islet in embryo pancreas.

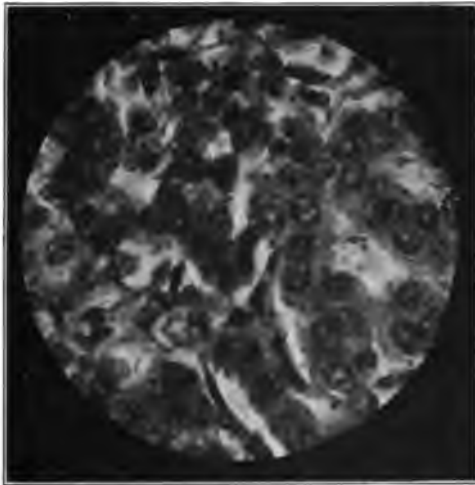


FIG. 65.—(H.187 Univ. of Minn. Collection.) Oil immersion microphotograph of islet cells, embryo 158 mm.

islet cells appear in the connective tissue along the small ducts. Pearce found masses of cells which he identified as islet cells in an embryo of 54 mm. In the section of one embryo, \* 158 mm. in length, in which I

\* University of Minnesota, Collection No. H.187.

examined the ducts, acini and islets were well developed. The islets stand out clearly in the loose connective tissue near the ducts. They are circular masses, the cells of which are not well differentiated. As

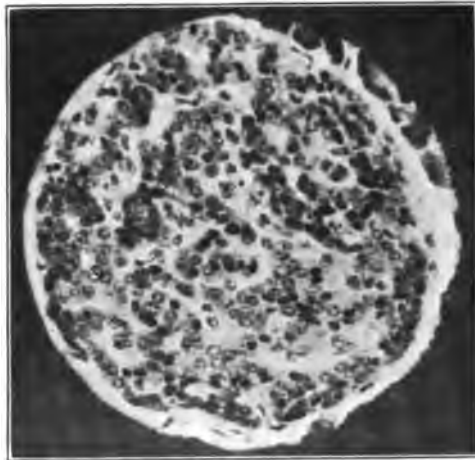


FIG. 66.—(A135776). Microphotograph of islet in an infant aged eight months.

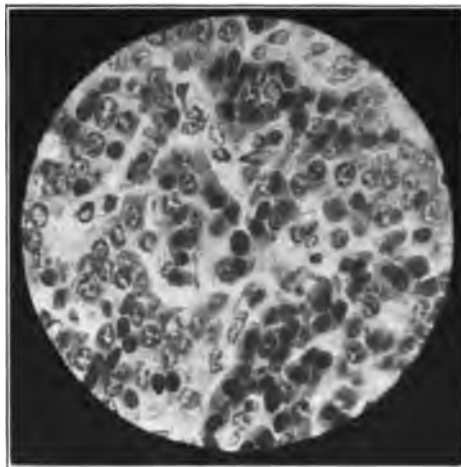


FIG. 67.—(A135776). Oil immersion microphotograph of islet cells in an infant aged eight months.

the glandular tissue grows into the connective tissue it envelops the islets. The connective tissue is derived from the mesodermal tissue of the dorsal mesentery (Fig. 62).

## HISTOLOGY

The embryology of the pancreas has been sufficiently studied in man and in species of lower vertebrates to establish the fact that all the histologic units develop from the same anlagen.

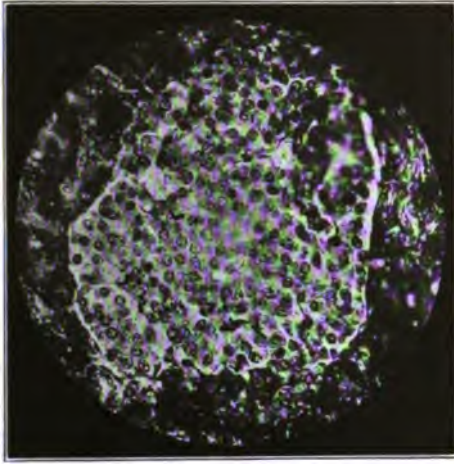


FIG. 68.—(A122722). Microphotograph of islet in pancreas of adult.

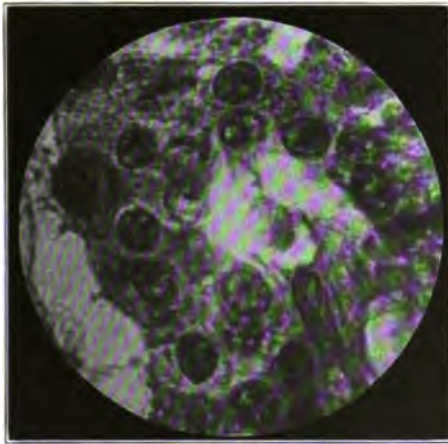


FIG. 69.—(A122722). Oil immersion microphotograph of islet in pancreas of adult.

The pancreas is a "mixed" epithelial gland composed of three separate and distinct histologic units each made up of differentiated, specialized epithelial cells:

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1. The pancreatic ducts (of Wirsung, Santorini, the interlobar and intralobular ducts, and the anastomosing tubules of Bensley).
2. The alveolar glands.
3. The islets of Langerhans (Fig. 63).

*The pancreatic duct system.*—The duct system in the pancreas is made up of one large duct, the duct of Wirsung, and an accessory duct, the duct of Santorini. From these ducts numerous highly branched tubules ramify the organ. The duct of Wirsung passes from the duodenal portion of the organ, where it opens into the ampulla of Vater, to the splenic portion. Throughout its entire length the first division of the tubules opens into it. These primary branches do not

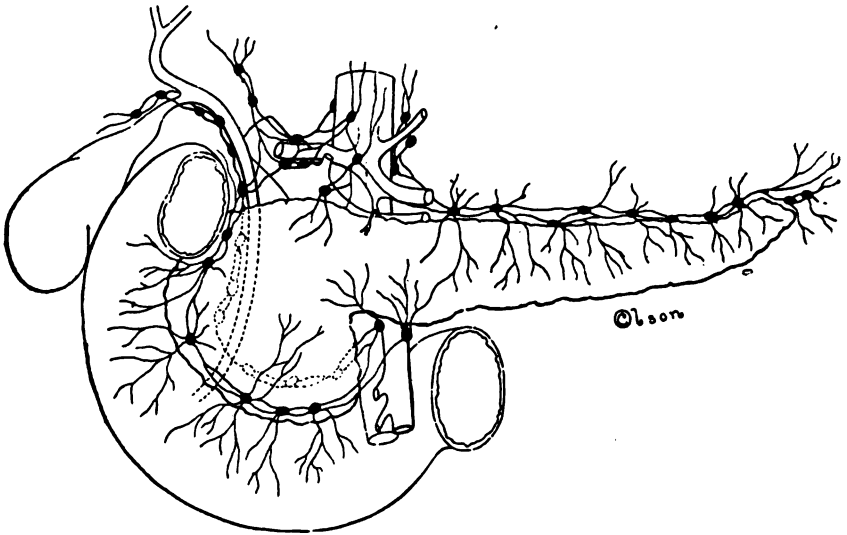


FIG. 70.—Diagram of peripancreatic lymphatic glands.

enter directly; they pass obliquely through the connective tissue of the duct of Wirsung for a short distance. The terminal branches are rather tortuous; Bensley has shown that they have many anastomosing tubules. The main ducts (Wirsung and Santorini) are lined with a single layer of high columnar epithelium on a fine membrana propria; in some sections it is thrown up into folds. In the interlobular and intralobular and anastomosing tubules the epithelium is a single layer of columnar cells, gradually diminishing in height in the terminal branches.

*The alveolar glands.*—Projecting out from the terminal ends of the

tubules are the alveolar glands. These are branched tubular glands lined with a single layer of large secreting cells, pyramidal in shape, the apex of which points into the lumen of the acinus; the base, near which is a large circular nucleus, lies on a membrana propria. The cytoplasm is divided into two zones, granular and homogeneous; the granular zone at the apex is made up of the zymogen granules in a faintly staining protoplasm; the homogeneous zone is in the basal portion of the cell. The zymogen granules in the granular layer and the mitochondrial filaments in the homogeneous layer may be studied only by the use of special fixation and staining. The secreting acinic



FIG. 71.—(A36163). Microphotograph of duodenal ulcer perforated onto pancreas showing marked connective tissue reaction in area of localized pancreatitis.

cells receive their blood supply from a capillary network in the membrana propria.

*The islets of Langerhans.*—These islets are small circumscribed masses of epithelial cells distributed throughout the entire organ, although they are more numerous in the splenic portion. Most of the islets are spherical, from 0.2 to 0.3 mm. in diameter, but they may be oval in shape. They have no duct connection, either with the pancreatic tubules or with each other, but lie in close relationship to the tubules. The texture of the connective tissue separating them from the acini is very delicate. The arteries supplying the islets form a rich capillary cluster. The vessels do not enter through a hilus. Each islet has a number of small capillaries which pass in from the connective

tissue at different points on the surface. The arrangement of the efferent blood stream is the reverse.

The islet cells are of two varieties, A and B. The A cells are the larger; they have a large elliptical nucleus with the chromatin in one

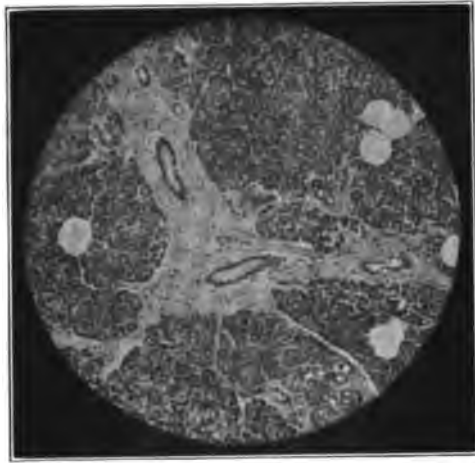


FIG. 72.—(A611333). Microphotograph. Chronic pancreatitis. Interlobular fibrosis most marked.

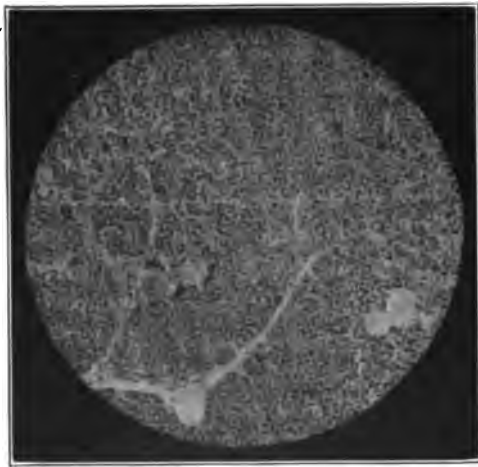


FIG. 73.—(120520). Microphotograph. Chronic pancreatitis. Interacinar fibrosis most marked.

or two round clumps. In the cytoplasm there are many small granules. The smaller B cells are more numerous; they have a central nucleus which is circular and contains a larger amount of chromatin.

Their cytoplasm is packed with small granules. These cells may be differentiated from one another and the granules stained only by the fixation and staining methods of Lane. In the sections the cells are

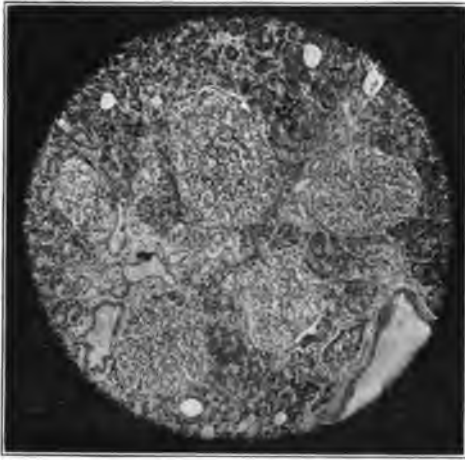


FIG. 74.—(A58947). Microphotograph of hypertrophic islets. Stage of pancreatico-primary-adenocytoblasia.

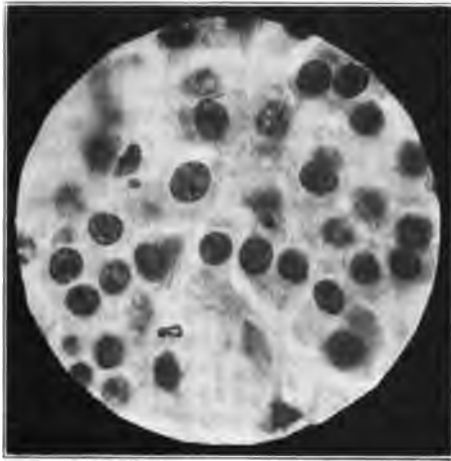


FIG. 75.—(A116521). Oil immersion microphotograph of hypertrophic islet. State of pancreatico-primary-adenocytoblasia.

seen in irregular masses, in single, or in double cords. They lie in a delicate connective tissue among the loops of the capillary cluster (Figs. 64, 65, 66, 67, 68, and 69).



*Blood vessels.*—The blood supply to the pancreas is through the splenic, hepatic, and superior mesenteric arteries. The main trunk of the splenic and hepatic arteries each sends a number of branches. The superior pancreaticoduodenal and the inferior pancreaticoduodenal supply the head with a number of branches. The veins which are tributaries of the portal system follow the arteries.

*Lymphatics.*—The lymphatics drain into the splenic, anterior, and posterior pancreaticoduodenal groups (Fig. 70).

#### PATHOLOGY

*Technic.*—The pancreatic tissue was examined grossly; blocks cut from the duodenal, central, and splenic portions of the pan-

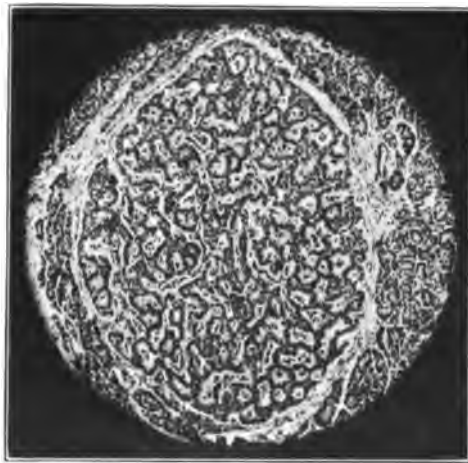


FIG. 76.—(A50276). Microphotograph of hypertrophic islet. Stage of pancreatoc-secondary-adenocytoplasia.

creas were sectioned and stained for microscopic study. The gross specimens had been preserved in neutral 10 per cent formalin solution. Blocks for microscopic study are preserved in 10 per cent formalin solution, Zenker's fluid with acetic acid, and Bensley's formalin-Zenker solution. Blocks from all the specimens which are preserved in formaldehyde solution were placed in a weak aqueous solution of ammonia for twenty-four hours and a few drops of strong ammonia added to the weaker alcohols when the tissues were being dehydrated; those preserved in Zenker's fluid with acetic acid and

Bensley's formalin-Zenker were dehydrated in the usual manner. The blocks were embedded in paraffin and several slides from each block were cut in series for the routine microscopic examination.

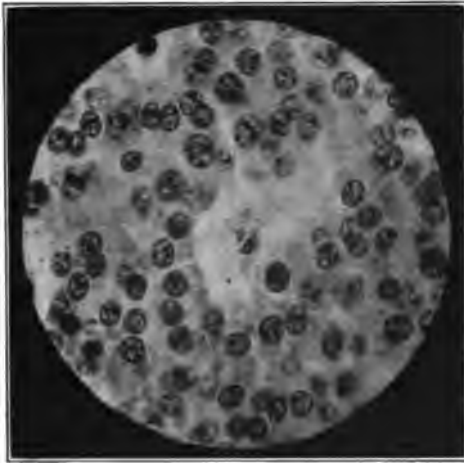


FIG. 77.—(A50276). Oil immersion microphotograph of epithelial cells in hyper-trophic islet. Stage of pancreatico-secondary-adenocytoblasia.

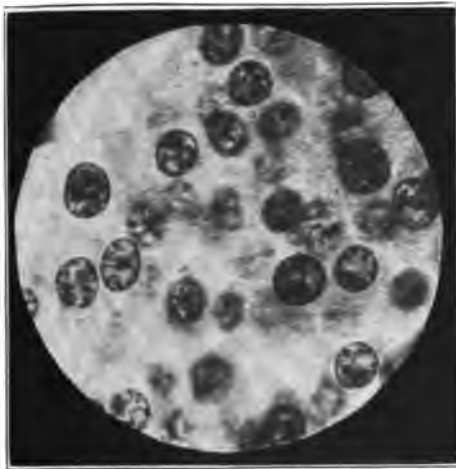


FIG. 78.—(A50276). Oil immersion microphotograph of epithelial cells in hyper-trophic islet. Stage of pancreatico-secondary-adenocytoblasia.

Additional blocks and sections were cut when needed. A few frozen sections were made. Some sections were stained with Ehrlich's hematoxylin and eosin and Goodpasture's acid polychrome-methylene

blue and eosin. Others were stained with phosphotungstic acid hematoxylin and Bensley's brasilin-water blue to differentiate the islet epithelium from the acinic epithelium. The blocks of tissue

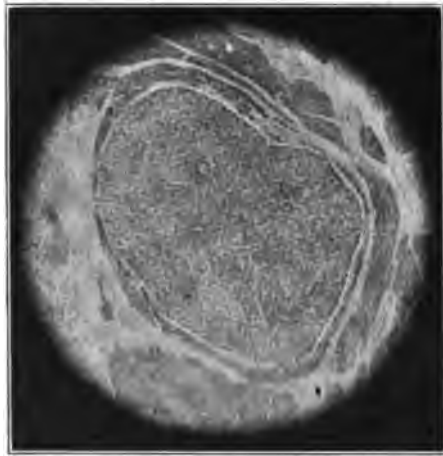


FIG. 79.—(A26398). Microphotograph of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule. Stage of pancreatico-tertiary-adenocytolasia.

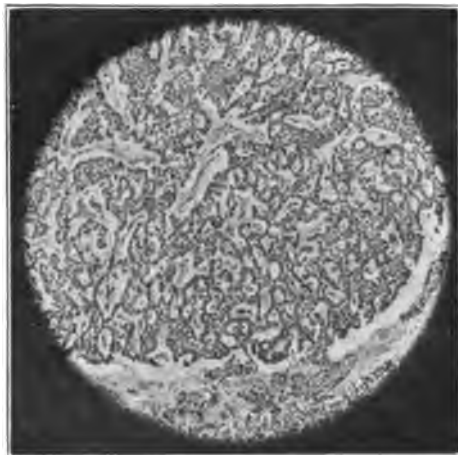


FIG. 80.—(A26398). Microphotograph of periphery of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule. Stage of pancreatico-tertiary-adenocytolasia.

which had been preserved in formaldehyde and treated with ammonia could be differentiated by these stains also.

*Chronic pancreatitis.*—Chronic pancreatitis is an almost if not

a constant finding in association with gastric and duodenal ulcer; it is most marked, however, in the duodenal portion of the organ. The amount of pancreatic involvement and the degree of inflammatory

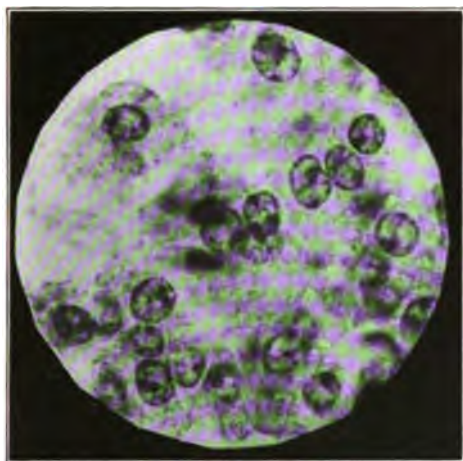


FIG. 81.—(A26398). Oil immersion microphotograph of islet cells showing hypertrophic, hyperplastic epithelial cells. Stage of pancreatico-tertiary-adenocytoblasia.

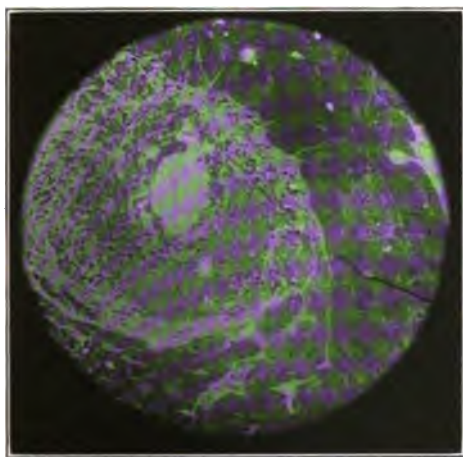


FIG. 82.—(A50276). Microphotograph of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule. Stage of pancreatico-tertiary-adenocytoblasia.

reaction are dependent on the location and duration of the ulcer and the severity of the acute exacerbations. When the gastric or duodenal ulcer perforates on to the pancreas and an area of the pancreas becomes

the base of the ulcer the marked local pancreatitis which develops gradually changes from an acute to a chronic form (Fig. 71). In addition there is usually a diffuse pancreatitis (Figs. 72 and 73). The



FIG. 83.—(A50276). Microphotograph of periphery of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule. Stage of pancreatico-tertiary-adenocystoplasia.



FIG. 84.—(A50276). Microphotograph of islet cells showing hypertrophic, hyperplastic epithelial cells. Stage of pancreatico-tertiary-adenocystoplasia.

pancreatitis is manifested either by a lymphocytic infiltration or by fibrosis extending into the interlobular, interacinar and periductal connective tissue.

*Hypertrophy of the islets observed in the series of cases studied.* In the microscopic examination of sections of the pancreas from the 262 cases that were selected for this study, hypertrophy of the islets in connection with a chronic pancreatitis was found in 48 cases. When the histories of these 48 cases were examined, two important discoveries were made: first, none of them showed glycosuria in any of the urinalyses of twenty-four hour specimens made while the patients were under observation and examination; second, 79.3 per cent of these were found to be cases in which a gastric or duodenal ulcer was found at operation or at necropsy. In the series of 262 cases which was selected for this study gastric ulcer



FIG. 85.—(A142013, Aut. 269-1915). Advanced carcinoma of pancreas.

was found in 71; in seventeen (25 per cent) the islets showed hypertrophy. Duodenal ulcer was found in 61 cases; in nineteen (31 per cent) the islets showed hypertrophy. Gastric and duodenal ulcer were found associated in 11 cases; in two (18.1 per cent) the islets showed hypertrophy. Hypertrophy of the islets was also observed in 6 cases of gastric carcinoma, 2 cases of carcinoma of the rectum, one case of carcinoma of the sigmoid, and one case of cyst of the pancreas.

Hypertrophy of the islets was observed grossly and in section from all portions of the gland. Grossly the largest ones appeared as creamy

white bodies. Microscopically the close relationship of these hypertrophic islets to the ducts was very noticeable. They varied from slightly above normal to twenty times their normal size, the largest islet measuring 6 mm. in its greatest diameter.

*Microscopic pathology of hypertrophic islets.*—There is a great variation in the size of the hypertrophic islets; they vary from 0.5 mm. to 6 mm. in diameter. Most of them are round or oval, on section, although many do not conform to this shape. In a few cases examination of all the sections showed only a few hypertrophic islets

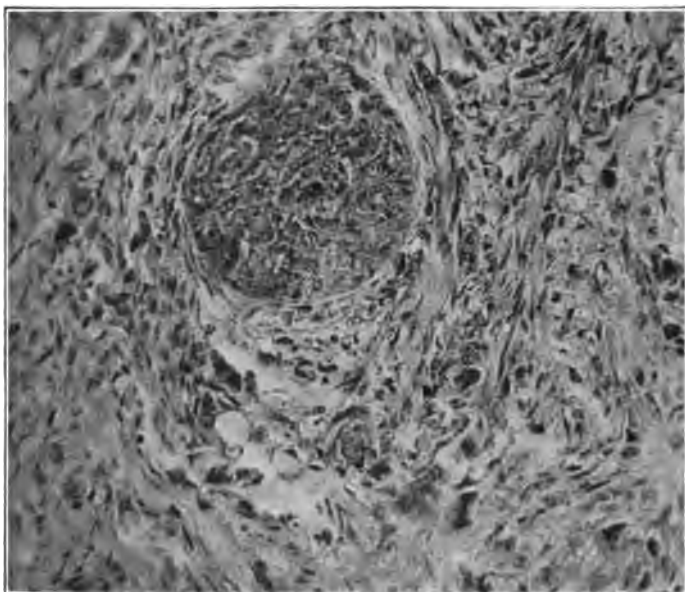


FIG. 86.—(A142013, Aut. 269-1915). Microphotograph of section from advanced carcinoma of pancreas showing degenerating epithelial cells in dense fibrous tissue and fibrosis of islet.

in each case; usually they were found in greater numbers. They are found in sections from all portions of the pancreas but in a few cases all which were observed were in the duodenal portion. Connective tissue in the islets is always increased and the capsule surrounding the islet is always thickened (Fig. 74). Hypertrophic and hyperplastic epithelial cells are found in these islets and in a few migration of these hyperplastic epithelial cells takes place; they pass through the three successive stages of neoplasia.

*Primary cytoplasia.*\*—The arrangement of the cells in the islets in short single and double cordons and masses between the capillary loops is similar to the normal. Most of the epithelial cells of these islets are differentiated; some are hypertrophic and the outline of the cytoplasm in these is not well defined (Fig. 75). These islets have a thickened connective tissue capsule and a diffuse fibrosis throughout. They are 0.5 mm. to 1 mm. in diameter. The capillary blood vessels have slightly thickened walls. No leukocytes or lymphocytes are

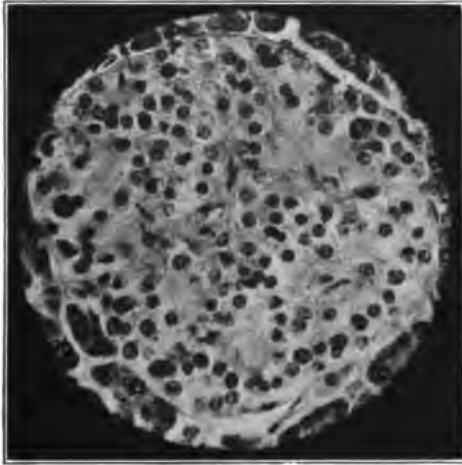


FIG. 87.—(A122622). Microphotograph showing hyalinized fibrosis of islet.

to be seen nor is there any other evidence of an inflammatory process of the islets except a fibrosis.

*Secondary cytoplasia.*—The cordons formed by the epithelial cells are more marked than in the normal islet. Most of the cordons are formed by single rows of epithelial cells, a few by double rows. In the sections these cordons follow the contour of the blood vessels and where the vessels are sectioned transversely the cordons encircle them. The epithelial cells are undifferentiated or partially differentiated. Some of the undifferentiated cells are hypertrophic. The

\* MacCarty's terminology of stages of neoplasia:

Primary cytoplasia = Hypertrophy of regenerative cells plus presence of differentiated cells.

Secondary cytoplasia = Hyperplasia of regenerative cells plus absence of differentiated cells, with or without partial differentiation.

Tertiary cytoplasia = Hyperplasia of regenerative cells plus migration, with or without partial differentiation.



number of epithelial cells has increased markedly but all the cells are confined within the connective tissue capsule (Figs. 76, 77 and 78). Some of these hypertrophic islets with hyperplasia of the epithelial cells are very large (0.6 mm. to 1.5 mm.). The capsule is of dense fibrous connective tissue and fibrosis is diffuse throughout the islet. The capillary blood vessels have increased in proportion to the size of the islets and the vessel wall is thickened. There is no evidence of inflammation except fibrosis.

*Tertiary cytoplasia.*—The cordons are not well defined; most of the cells are in masses. The epithelial cells are undifferentiated; some, however, in some islets show partial differentiation. They are hypertrophic and hyperplastic, there being a marked increase in the size and number. In the center of some of the islets there is an area of cellular debris as the result of cellular disintegration; a few nuclei can be identified in this area. Migration of the epithelial cells through the connective tissue may be seen at the periphery. This migration of the epithelial cells is evidence of a carcinoma (Figs. 79 to 84). These islets are very large, the largest being 4mm. by 6 mm. Proliferation of the connective tissue is very marked throughout the islet and the capsule is thick and densely fibrous. Bands of fibrous tissue pass out from the capsule of the islet into the interacinar and interlobular connective tissue. The blood vessels are very large, but their size is in proportion to the size of the islet, and their walls are thickened.

#### DISCUSSION

The islet areas in the pancreas were first described by Langerhans, who considered them to be the end apparatus of nerve fibers. From the collective embryologic, cytologic, and histologic studies of later workers, foremost among them Renaut, Laguesse, Opie, Lane, Lewis, Thyng, Dewitt, and Bensley, it has been well established that the islets are, histologically, a definite epithelial unit of the pancreas developed from the epithelium of the primitive anlagen, without duct connection, with a rich capillary blood supply, and a hormone-secreting function.

Hypertrophy of the islets, and adenomas of the islets, are the only conditions reported in the literature which could be considered precancerous. Hypertrophy has been reported mostly in connection with diabetes. It is not characteristic of diabetes, however, nor is it

to be found in all cases of diabetes. Nichols, Helmholtz, and Cecil have reported cases of a single hypertrophied islet in the pancreas. Nichols and Helmholtz each considers his case to be an adenoma while Cecil reports his case an hypertrophy of the islet.

After reviewing the literature I find that most writers classify carcinoma of the pancreas either as alveolar or canalicular.

In 1903, Fabozzi reported his study of the pancreatic tissue taken from 5 patients who had died from carcinoma of the pancreas and tried to establish from these the histogenesis of carcinoma of the pancreas. His deduction is that all carcinomas of the pancreas have their origin in the islets. His illustrations are diagrammatic, and his descriptions are not sufficiently conclusive to be accepted by later writers.

It is not reasonable to assume that all neoplasms in a mixed gland, like the pancreas, originate in one only of its three epithelial units. It is more logical to assume that a neoplasm may originate in any one of the epithelial units, the ducts, the acini, or the islets. From a biopathologic point of view the histogenesis of neoplasia of the pancreas should be studied in each of these. Under suitable pathologic conditions, each epithelial unit could be expected to produce undifferentiated cells from its germinative tissue; but the study must be made from the tissues which show the changes antecedent to carcinoma. When neoplasia is well advanced or has caused death, it is impossible to establish the site of origin or the successive pathologic changes from the tissue removed at operation or at necropsy; it is because pathologists have tried to prove the histogenesis from tissue removed at necropsy, after malignancy has caused death, that the histogenesis of carcinoma of the pancreas has not been established (Fig. 85). In a microscopic study of advanced carcinoma of the pancreas we find small masses of cells in the dense fibrous connective tissue. In their form and arrangement they may resemble small ducts, or acini, but if carefully scrutinized they will prove to be groups of degenerating cells. They are epithelial cells, but whether they are degenerating acinic cells or degenerating cells of neoplasia cannot be determined (Fig. 86).

The histogenesis of carcinoma of the pancreas must be studied from portions of the pancreas which are too small to be recognized in the gross specimen as carcinoma. For this reason I selected for the study of the early neoplastic changes a series of cases which show

chronic inflammation. In the course of the investigation I found a definite hypertrophy and hyperplasia of the islets of Langerhans. This condition was found in about 25 per cent of the cases of chronic interacinar and interlobular pancreatitis which was associated with chronic gastric and chronic duodenal ulcer. In these hypertrophic islets hypertrophy, hyperplasia, and migration of the cells were observed.

In the hypertrophic islets I found hypertrophic differentiated cells. Accompanying this cellular hypertrophy the connective tissue within and surrounding the islets had increased to protect the adjacent cells from encroachment.

In similar islets I sometimes found also hyperplasia of undifferentiated epithelial cells. These undifferentiated cells, however, are distinctly confined within the dense capsule of the islet.

In some of the hypertrophic islets I found hyperplastic undifferentiated cells migrating through the capsule, a condition which is undoubtedly carcinoma.

These three graphic descriptions apparently represent the stages of neoplasia as described by MacCarty in other epithelial tissues.

Simple fibrosis and sometimes hyalinized fibrosis were the only purely inflammatory reactions found in this series (Fig. 87).

The biologic reactions in the epithelial cells of the islets in the pancreas conform to those that have been observed in epithelial cells in other tissues. MacCarty has pointed out that each organ should be studied from the standpoint of each histologic unit; that each histologic unit must be considered alone from the standpoint of regeneration in all its phases; and that each phase should be named with a descriptive term applicable to that tissue; these biopathologic reactions of the epithelium of the islets in the pancreas might then be described as follows:

$$\text{Pancreatico-} \left\{ \begin{array}{l} \text{primary} \\ \text{secondary} \\ \text{tertiary} \end{array} \right\} \text{ adeno-cytoplasia}$$

These descriptive terms are expressive of the successive biopathologic reactions in the regeneration of cells in neoplasia in the islets of the pancreas.

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# THE UTILITY OF THE RUBBER TUBE IN INTESTINAL SURGERY\*

D. C. BALFOUR

The difficulties which not infrequently confront the surgeon<sup>1</sup> in carrying out operations on the large and small intestine are to a considerable degree overcome by his familiarity with the established principles of intestinal surgery, his ability to employ technical methods of proved value and to utilize the various mechanical devices which, in the development of the surgery of the gastro-intestinal tract, have been devised to meet special conditions arising during the course of the operation. Of such mechanical devices the rubber tube deserves, I believe, more general and favorable recognition than is at present accorded it. Its usefulness in certain intestinal operations has been so evident, and the result of such operations so gratifying, that it seems advisable again to draw attention to these facts by presenting abstracts of case reports which are representative of some of the conditions under which we have employed the rubber tube, and which illustrate the utility of the tube in intestinal surgery.

Such operations as resections of the sigmoid, rectosigmoid juncture, or upper rectum for malignancy, are and always will be frequently of considerable technical difficulty and of relatively high risk. In our experience in the Mayo Clinic the rubber tube has been an important factor in minimizing such difficulties and risks, and it was in certain cases in this group that the tube was first employed as an aid in accomplishing a safe axial anastomosis. Its value under these circumstances had been recognized for several years; Rutherford Morison, Lockhart Mummery, and other English surgeons, were early advocates of its merit, and it had been employed in the Mayo Clinic for some time previous to 1910, when I described the technic of "tube-resections" of the sigmoid as then carried out in the clinic. Since that time certain modifications in the operative technic then described have been found advantageous; and, as is so frequently true, the higher efficiency which

\* Reprinted from Surg. Gynec., and Obst., 1920.

has come from such improvement in technical methods has made possible not only better results, but also a definite increase in "operability." We have accepted as operable and successfully removed malignant tumors of the lower sigmoid or upper rectum, the operability of which,



FIG. 88.—Beginning of posterior suture line.

without the aid of the tube in the operation, would be at least highly questionable.

The tube used in such cases is  $\frac{3}{4}$  inch in diameter with  $\frac{1}{2}$  inch caliber with a lateral eye about 1 inch from its upper end. The resection having been made, the tube is introduced through the open end of the lower

segment and passed by the surgeon downward through the rectum and anus; it is there secured by an assistant and tracted upon until the upper end of the tube is brought below the level of the cut end of the lower segment. The two ends of bowel are now approximated, properly aligned, and fixed by a stay suture in the middle of one lateral

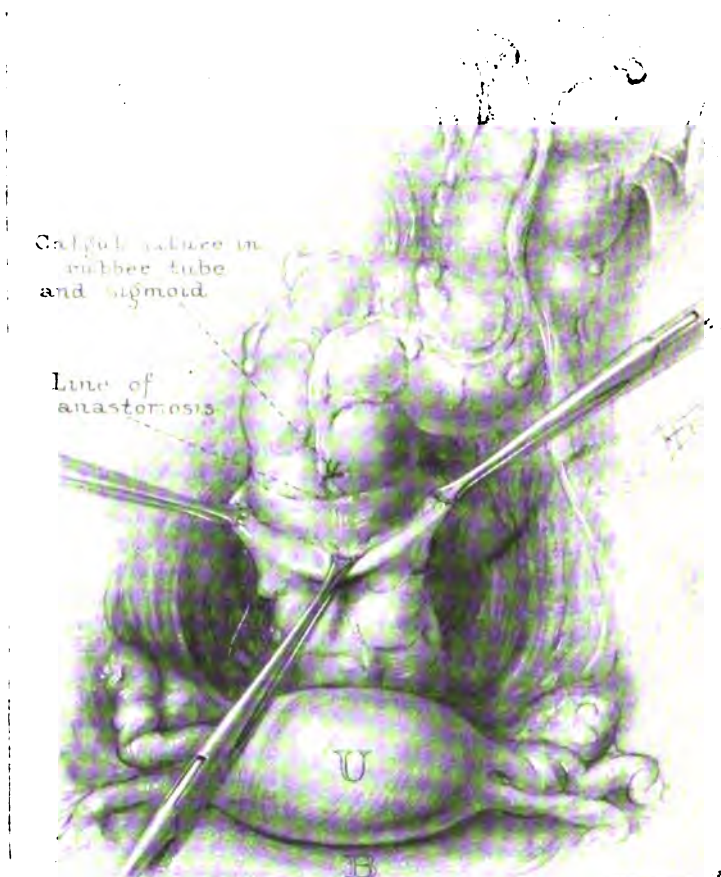


FIG. 89.—Anastomosis completed; bowel ready for invagination.

wall and a second stay suture at a corresponding point at the opposite side. At this latter point a heavy chromic catgut suture is begun. This suture is introduced from the mucous side and includes the mucous and muscular layers of the intestinal wall and is continued posteriorly in this manner until the stay suture, which was first placed, is reached. Our experience has been that, if No. 2 chromic catgut is used and special

care is taken to approximate the mucous membrane so that it does not extrude outside the bowel wall, a most satisfactory closure posteriorly can be secured (Fig. 88.) When the circular anastomosis is completed in the usual manner by a continuation of this chromic catgut suture, the tube is passed up the bowel by the assistant until it reaches a point



FIG. 90.—Final relationship of the bowel and rubber tube (diagrammatic).

from 3 or 4 inches to 1 foot above the level of the anastomosis. The correct height of the tube must be gauged by the ease with which it takes its position in the upper segment. The tube, resting in its best position in the upper segment, is secured by a suture of heavy catgut placed close to the anastomosis line, so that the suture will be invaginated with the anastomosis later (Fig. 89). The invagination, which we believe to be



a very important feature of the operation, is then made by grasping the lower segment with fine toothed forceps at a point of about 1 inch below the line of anastomosis; and by means of these forceps the lower segment is supported while the assistant pulls downward on the tube until the anastomosis line is drawn into the lower segment, and the anas-

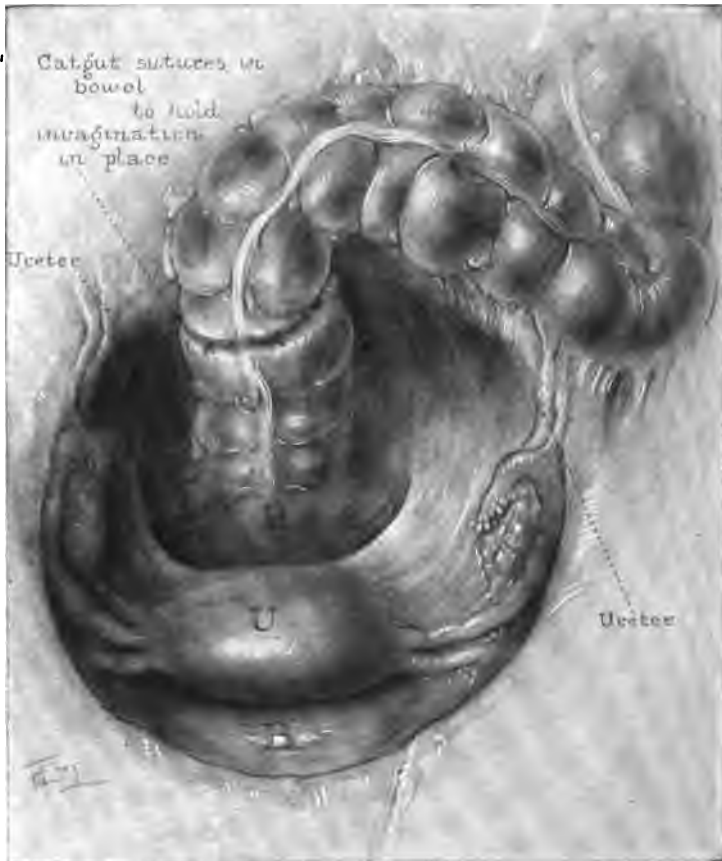


FIG. 91.—Operation completed.

tomosis is completely covered (Fig. 90). The loose ring of the lower segment is then fixed to the upper segment by three or four interrupted sutures (Fig. 91). The bowel at the site of the anastomosis then has the same appearance as that of a small intussusception. In some cases it is not possible to produce such an invagination because of the extent of the resection, and in some instances it is not even possible perfectly

to unite the two ends of the bowel over the tube. It is surprising, however, to observe the excellent immediate and ultimate results in such unsatisfactory cases; and even in cases in which a visible defect in the line of the anastomosis was present (usually on the posterior side) a satisfactory convalescence has ensued. When a fecal fistula does occur spontaneous closure can be anticipated. In the majority of cases it is quite safe to close the abdomen without drainage.

#### REPORT OF CASES

##### RESECTION FOR CANCER OF THE SIGMOID

Case 1 (A261807). Miss E. E. H., aged 26, presented herself at the clinic Feb. 27, 1919. She gave a history of having had symptoms suggestive of a partial obstruction of the large bowel, beginning December, 1918; these symptoms became more definite and severe until January, 1919, when obstruction was complete and operation imperative. The surgeon, finding the obstruction in the sigmoid due to a mass apparently malignant, considered any attempt to remove the tumor inadvisable and performed a colostomy. Six weeks later the patient arrived at the clinic in fairly good physical condition and with only a moderate weight loss. Examination showed a well functioning colostomy and a mass in the left pelvis which could be easily outlined, both by vagina and by rectum. An x-ray examination revealed an obstruction of the colon about 5 inches above the rectosigmoid. The absence of any evidence of metastasis, the good condition of the patient, and, particularly, our previous experience in such cases, led us to advise exploration. March 6, 1919 an abdominal exploration was made (W. J. Mayo). An incision 1 inch to the left of the midline gave easy access to the growth in the sigmoid. The growth proved to be a constricting cancer, of the napkin ring variety, situated about 4 inches above the rectosigmoid juncture. Resection seemed feasible and, after the separation of the colostomy from the abdominal wall, a portion of the sigmoid, including both the colostomy and the growth, was removed. Because of the firm attachment of the sigmoid to the left ovary and tube, it was necessary to remove both of these structures. An end-to-end union was then accomplished over a tube in the manner described above; the former abdominal incision was widely excised before closing, and two rubber tissue drains were carried down to the site of the anastomosis. The patient had a most satisfactory convalescence; the

tube was removed on the eighth day, and both the new incision and the former incision were healed when she left for home three weeks after operation. Her present condition is excellent; and although malignancy at such an age is associated with a gloomy prognosis, some prospect of cure can be entertained.

Case 2 (A185641). Mrs. H. C. L., aged 41, came to the clinic Feb. 14, 1917 giving a history of symptoms of obstruction of the sigmoid over a period of the past twenty-two months. A mass could easily be identified in the suprapubic region, and on bimanual examination it proved to be in the left pelvis. Exploration was carried out Feb. 24, 1917 (J. C. Masson). A cancer of the left rectosigmoid was found, the mass being adherent to the uterus, the left broad ligament, and the left lateral wall of the pelvis. It had all the characteristics of a malignant process and was clearly inoperable. Colostomy was done and radium treatments advised. In January, 1918 the patient had 1600 mg. hours, in August, 1900 mg. hours, and in January, 1919, 4200 mg. hours. At each examination the mass was distinctly smaller, with a corresponding decrease in symptoms, such as pain and discharge. In November, 1919 the patient returned to the clinic, requesting to have the colostomy closed. She was in excellent general health, weighed 224 pounds, and the absence of symptoms showed, at least, that the former malignant mass was inactive. On examination of the lower segment through the colostomy opening, the finger could not be passed because of the contraction which had taken place beyond the site of the former growth. Bimanual examination showed a small nodular movable mass high in the pelvis. A second operation was, therefore, performed November 15 (J. C. Masson). The portion of the sigmoid in which the radium had been used was in an atrophic condition, with marked thickening of the intestinal walls and, because of the extent of this induration, it was necessary to remove about 14 inches of the colon; the resected portion contained the colostomy and the thickened bowel. The operation was unusually difficult because of the short lower segment, the patient's obesity, and the fixity of the segments of intestine. The anastomosis, however, was finally accomplished over a rubber tube by interrupted sutures of chromic catgut, the bowel being intussuscepted about 1 inch. The anastomosis was carefully protected by suturing the omentum over it, and the uterus fixed to the anterior aspect of the anastomosis. It was difficult to determine from the gross appearance of the sigmoid whether or not any active cancer cells were present;

and it was very interesting, important, and gratifying to find that repeated pathologic examinations did not show any evidence of malignancy. The wound was closed without drainage; the patient made a satisfactory convalescence, and left for her home Dec. 17, 1919.

#### RESECTION FOR DIVERTICULITIS OF THE SIGMOID

**Case 3 (A35613).** Mrs. J. G. F., aged 52, had had an exploratory operation elsewhere in March, 1909 because of symptoms referable to the sigmoid region; and at the exploration three diverticula were observed in the sigmoid over an area of about  $2\frac{1}{2}$  inches. A conservative operation was done, but leakage developed at the site of the operation and a fecal fistula persisted and was chiefly the reason for which the patient presented herself at the clinic. Exploration (the closure of the fistula being the primary object) was clearly advisable, and was done March 24, 1910 (C. H. Mayo). A diverticulitis of the sigmoid was found which was adherent to the small intestine and a small abscess in the abdominal wall. After the separation of these various adhesions, the sigmoid was resected and an anastomosis carried out by the tube method, as described above. The patient made a most satisfactory convalescence and has remained well.

The tube, then, can be used in certain cases of diverticulitis in a manner similar to that described, but it is not employed so frequently as in operations for cancer of the sigmoid because of the fact that the mass in diverticulitis is usually in the upper sigmoid and can be mobilized without much difficulty. Resection, therefore, is usually made in diverticulitis by the Mikulicz three-stage method, and when immediate axial anastomosis is indicated the procedure is not particularly difficult.

In cases in which primary resection is advisable, a satisfactory and safe method to employ is that suggested by C. H. Mayo. After a circular anastomosis has been accomplished in the usual manner, the entire anastomosis line is drawn through an opening made at a suitable point in the omentum and attached to the peritoneum at the incision in such a way that the suture line shows after the peritoneum is closed. The wound can then be closed without drainage, or, if preferred, with mural drainage. This method has given us most satisfactory results. The general abdominal cavity is effectively walled off by the omentum; and, should any leakage occur, such drainage has no difficulty in finding its way into the incision.

## REPAIR OF FECAL FISTULA

Case 4 (A291805). Mrs. M. A. H., aged 46, came to the clinic Oct. 3, 1919 because of a fecal fistula. An abstracted history shows that she had been perfectly well until about two years before, when she had an attack of severe abdominal pain in the left lower abdomen lasting three or four hours, which was to some extent relieved by hot applications. Until May, 1919 she continued to have these attacks, which usually lasted about three or four hours and occurred at intervals of three or four months. In May, 1919 an attack developed as usual apparently, but could not be relieved by the usual measures, and after it had continued for about a week the patient was operated on elsewhere and 6 inches of the sigmoid resected, anastomosis being made by means of the Murphy button. The pathologic report made at the time on the specimen excised was "small round-cell sarcoma." The patient developed a fistula three days after the operation, suffered a great deal of general pain throughout the abdomen, and failed to show any improvement. In the physical examination carried out at the clinic on her arrival the chief finding was a mass in the right pelvis, apparently on the rectal shelf, of a rather nodular character, and considered to be a recurrence of the malignant process. It seemed advisable to explore, however, and to close the fistula if feasible. Exploration was carried out Oct. 24, 1919 (W. E. Sistrunk). Fortunately no evidence of malignancy could be demonstrated. The mass, which could be palpated before operation, proved to be an induration due to scar tissue which appeared to be the result of the previous operation. The dissection of the fistulous tract led to the site of the former operation and at this point in the sigmoid there was considerable thickening and the bowel was firmly adherent to the posterior wall of the uterus. Having liberated the bowel it was necessary to excise the segment of indurated sigmoid, which was a matter of some difficulty because of the firm inflammatory changes which had taken place. Anastomosis was made over a tube in the typical way, the tube being of particular assistance because of the fixity of the segments of bowel. The patient had a very satisfactory convalescence; a slight difficulty in the passage of fecal matter through the tube was overcome by the manipulation of a catheter through the rectal tube.

## USE OF TUBE ALONE IN CHRONIC AND SUBACUTE OBSTRUCTION

Case 5 (A177159). Mrs. J. D., aged 39, came to the clinic Nov. 6, 1916, complaining of attacks at irregular intervals of great abdominal distress due to an enormous distention of the abdomen with gas, with marked respiratory distress and cardiac pain. The attacks lasted frequently for from two to four days and were associated with a great deal of pain in the joints, especially the legs and shoulders. The patient was rarely entirely free from distress, although there were periods of from twelve to twenty-four hours when she was reasonably comfortable. Gas was expelled by rectum and through a fistula which existed in one of the abdominal incisions. The significant findings in the physical examination were the marked abdominal tympany, associated with visible intestinal peristalsis, four scars of previous abdominal operations, and general evidences of chronic infection, particularly in the joints of the feet and hands. The history leading up to the present condition was, chiefly, that four years before, following a severe attack of abdominal pain, the appendix, uterus, and some gallstones were removed elsewhere. Four weeks later it was necessary to do an ileo-sigmoidostomy because of obstruction. For the following years the patient had comparatively good health, but finally the intestine became obstructed again with formation of the fecal fistula and in May, 1916 she was again operated on. The fistula was closed and several loops of small intestine liberated. Following this operation the patient continued to have the symptoms which have been described. At operation Nov. 17, 1916 (E. S. Judd) a condition of general intestinal paresis was found. No point of definite obstruction could be determined. The small intestine, the cecum, and the transverse and descending colon were especially dilated. Because of the repeated operations and the general character of the obstruction, there was apparently no method of anastomosis by which a good result could with certainty be accomplished. A long rectal tube was passed per rectum through the existing anastomosis and continued for about 18 inches into the small intestine. Immediately a great quantity of gas and fecal matter passed, and it was decided to leave the tube in as long as possible in the hope that in the inevitable reformation of adhesions it would act in the rôle of a splint, and would support the bowel so that disabling deformity would not later occur. In a recent report the patient states that she has remained well and free from the intestinal disturbances for which the operation was carried out.

This case is a striking illustration of the value of the tube in those cases of chronic or subacute obstruction developing as a late result after repeated operations. When the tube can be employed in such cases the uncertainty which is so frequently felt by the surgeon is converted into an assurance that the segment of the intestine which has been supported by the tube will be so molded in the new mat of adhesions that future obstruction at that point is most unlikely to occur.

A case similar in some features to the foregoing, and having added points of interest, is the following:

Case 6. (A253595). Miss M. G., aged 20, came to the clinic Dec. 16, 1918 with a complaint of suffering daily from great accumulation of gas. This bloating usually came on between 4 and 6 in the afternoon; belching huge quantities of gas and slight vomiting usually gave partial relief. On two occasions the patient had attacks of abdominal cramps, apparently of great severity; these were also relieved when the gas was expelled. The patient was a rather unhealthy looking girl, but no evidences of gross disease could be determined. The abdomen was greatly distended and repeated purgation together with daily doses of belladonna failed to make any appreciable change in the distension. An x-ray examination showed a hugely dilated stomach, the bismuth remaining in the stomach for three days, and, although it was not possible to demonstrate positively that a pyloric lesion was present, surgical interference seemed indicated. Jan. 2, 1919 an abdominal exploration was done (D. C. Balfour). General exploration immediately confirmed the physical examination and the x-ray findings. The stomach was dilated to great size, the lower border reaching almost to the symphysis. No actual lesion could be found at the pylorus to account for the obstruction, it apparently being due to a mass of adhesions extending from the hepatic flexure to the duodenum and pylorus. Beside this tremendous dilatation of the stomach was a dilatation of the proximal half of the large bowel; this portion of the colon was doubled on itself by another wide band of adhesions, stretching from the middle of the ascending colon to the left half of the transverse colon. The proximal half of the colon was dilated to about 10 or 11 inches; the distal half was little more than normal size. The primary cause of these two conditions was not evident. In the absence of any visible lesion, the most plausible explanation seemed to be that either a congenital abnormality in the rotation

of the colon or some inflammatory process in childhood had left the colon in such a relationship that strong bands of adhesions were developed to the point of causing chronic obstruction and producing secondarily, from traction and trauma, the adhesions to the pylorus and duodenum. It seemed unwise, in any event, to attempt any prolonged investigation (because of the risk to the patient and the uncertainty of securing any important information) to learn the cause of the condition and this decision was strengthened by the fact that it was perfectly clear what was necessary to be done to meet the symptoms of which the patient complained. Gastro-enterostomy was first performed, followed by colocolostomy, the latter anastomosis being made between the tremendously distended cecum and the normal sigmoid. A large rectal tube was passed through the anus, rectum, and anastomosis until the end was about 1 foot above the level of the colocolostomy. The patient had a satisfactory convalescence, and has had complete relief from all the symptoms of which she complained.

#### RESECTION OF TRANSVERSE COLON

Case 7. (A263828). Mrs. N. W., aged 50, came to the clinic in March, 1919, chiefly because of discomfort which had begun in the epigastrium about three weeks before. This discomfort was usually associated with nausea, but vomiting occurred on only one occasion. The pain had never been severe and radiated only to the lower abdomen; temporary relief was secured on defecation. There had been no diarrhea nor abdominal colic. The patient stated that for a period of thirty years she had been distressed occasionally by a dull, bloated feeling in the epigastrium, usually immediately after taking food. The character of the distress, which had developed recently, its radiation to the lower abdomen, and the relief on bowel movement, suggested the possibility of intestinal obstruction. An x-ray of the colon demonstrated a cancer involving the hepatic flexure and the first part of the transverse colon. Exploration was, therefore, advised and carried out March 4, 1919 (J. D. Pemberton). A huge cancer of the transverse colon was found involving the glands in the transverse mesocolon. The growth had penetrated the serosa of the bowel and there was free fluid in the abdomen. A hard nodule at the anterior edge of the liver was excised and found to be a mass of gallstones which had become encysted following a perforation of the fundus of



the gallbladder into the liver substance. A resection of the transverse colon well away from the tumor was done and a direct end-to-end anastomosis made by the C. H. Mayo method, followed by a partial cholecystectomy with drainage of the gallbladder. At the completion of the operation, the anus was dilated and the rectal tube inserted and left in until the twelfth day. The patient made a satisfactory convalescence and has shown no evidence of a recurrence up to the present time.

It is advisable under certain conditions to provide a safety valve for the large intestine to prevent spasm of anal or rectosigmoid sphincters at a time when distension of the colon should be guarded against. A rectal tube serves such a purpose excellently and may often be resorted to in place of a colostomy or appendicostomy.

#### CLOSURE OF COLOSTOMY

Case (A253976). Rev. J. J. L., aged 48, came to the clinic December, 1918 because of a tumor in the left lower abdomen, attacks of pain, and partial obstruction for the last two years. The most recent attack was about one week before the examination in the clinic; the tumor had first been noted at this same time. Three months before he had had a severe hemorrhage of bright red blood; two other such spells of bleeding had occurred up to the time of his examination. A diagnosis of duodenal ulcer had been made elsewhere. The physical examination disclosed a hard mass which could be readily palpated both through the abdominal wall and bimanually. The x-ray confirmed the clinical diagnosis of cancer at the rectosigmoid juncture. The patient was operated on Dec. 12, 1918, (W. J. Mayo). A Mikulicz three-stage operation was done. A satisfactory convalescence ensued, and January 11 a clamp was applied to the spur of the sigmoid. The further convalescence placed this patient in the small group of patients in whom the bowel does not completely close after the routine three-stage Mikulicz operation, and April, 1919 he returned. An extraperitoneal closure of the colostomy was done over a Smithies stomach tube, which was introduced through the colostomy and pushed down through the anus, with the upper end about 2 inches above the point where the bowel was closed. This procedure completed the satisfactory result; the patient is at present apparently in perfect health.

Ineffective attempts to close colostomies are occasionally met with. Successful closing sometimes requires enough suturing of the opening in the bowel to constrict the lumen beyond what appears to be the limit of safety. The tube serves a useful purpose by preventing further contraction; and by conveying gases and fecal matter past the point of closure it gives the best possible condition under which healing may occur. In such cases the tube is introduced through the colostomy and passed out of the anus, leaving the upper end about 3 or 4 inches above the point of closure; it is removed in about ten days.

#### DISCUSSION

The foregoing abstracted cases illustrate the wide utility of a rubber tube in intestinal surgery, and I am convinced that further experience in extending its use will show that in the past we have occasionally overlooked its value because we have failed to recognize, or have forgotten, certain sound principles in the surgery of the gastrointestinal tract. Such principles could have been well carried out in certain cases by the use of the rubber tube. The mechanical functions of the tube are chiefly called upon in its employment in axial anastomosis, closure of colostomy, and fecal fistula repair. In such cases, its first service, as I have pointed out, is the prevention of gross leakage from an insecurely closed intestine. We have repeatedly met with cases in which the extent of bowel resected has been so great or the segment so fixed, or for both reasons, that approximation has been made difficult and an unsatisfactory union has resulted, on the mesenteric side particularly. When, however, such an anastomosis has been made over a good sized rubber tube the results have been unmistakable evidence that the tube, immobilizing the two segments of bowel as it does, gives protection against leakage, because of the security against undue tension, with the possible results of a weakened or ruptured suture line. Fecal fistulas which occur under such circumstances have been insignificant, as a rule healing spontaneously in a short time.

A further and most important mechanical function of the tube is observed in its actions as a splint. The danger of postoperative obstruction is always to be considered in those cases in which extensive scar due to previous operative interference or the adhesions of inflammatory exudates are present, for, in the inevitable reformation of ad-

hesions, the bowel may be fixed in such a manner that immediate or later obstruction is possible. In such cases, the tube within the bowel prevents any kinking or malposition which might occur in the reorganization of the exudative products which takes place in the first few days after operation. The value of the tube under such conditions is well illustrated in Case 5, in which the operation, which was anticipated to be of unusual difficulty, high risk, and dubious results, proved to be one of greatest simplicity, little danger, and complete success. It should be remembered that in the tube we have available a means of carrying the contents of the intestine through a point of actual, impending, or potential obstruction in the intestinal tract and that it can serve a most useful purpose in cases in which such danger is a possibility.

The possibility that the tube may be of service in certain disturbances in the neuromuscular mechanism of the intestinal tract is suggested by Case 6; although the immediate cause of the condition was not due to spasm, the primary cause may have been. During the past few years only have we gained any accurate knowledge of the neuromuscular mechanism of the gastro-intestinal tract. The original investigations of Gaskell, and the later work of Keith and Cannon have resulted in establishing certain facts, the most important of which in the present connection concerns the presence in the gastro-intestinal tract of nodes or controlling sphincters. Variations in the functioning of these sphincters cause disturbances in the section of the alimentary tract immediately under its control, with secondary disturbances in segments higher up. The extent to which such disturbances (that is, tonic spasm, atony due to sympathetic irritation, or irregular contractions due to parasympathetic irritation) may be responsible by reason of long continued action for actual disease in the gastro-intestinal tract and associated organs is yet to be determined. It is quite reasonable to believe, however, that abnormal functioning of such sphincters continued over a long period may, with the addition of other factors, result in disease processes which otherwise would not have occurred.

One of the most interesting anomalies in the intestinal tract is congenital dilatation of the colon or Hirschsprung's disease. No satisfactory explanation of the condition has been advanced, but from the character of the dilatations which occasionally occur in other portions of the intestinal tract it seems that chronic spasm of the recto-

sigmoid sphincter is an important factor in the development of the condition. If this be true, it is possible that in certain cases of Hirschsprung's disease, some method may be devised for forcible and repeated stretching of the sphincter at the rectosigmoid juncture, by instrumentation similar in principle to that so successfully used in cardio-spasm. Should such treatment be possible, a formidable operation could be avoided.

Another point of interest to be mentioned in this connection is the suggestion which has been made by Sampson Handley in his article on ileus duplex. He believes that certain cases of postoperative intestinal paresis with general peritonitis are due to spasm not only of the long sphincter in the terminal and pelvic ileum, but also of the sphincter in the termination of the pelvic colon (or at the rectosigmoid juncture), and that the percentage of recoveries from operations in such cases will be much higher if both the distended and obstructed ileum and colon are drained than if an enterostomy only is done. He accomplishes this procedure by an ileocolic anastomosis (ileum to ascending colon) combined with a cecostomy. In this way he makes certain that in the 33.33 per cent of cases in which both ileum and sigmoid are obstructed a safety valve is provided in the catheter colostomy. We have found that in some of these cases a tube introduced through the rectum could be passed beyond the point of spasm at the rectosigmoid, thereby avoiding the necessity of a colostomy. In certain cases of paresis, the anastomosis of ileum and colon, rather than enterostomy, should be given more consideration than has been afforded it in the past.

The various conditions under which we have employed the tube frequently necessitate serious and difficult operations in which any factor which adds to the safety of the operation and to the prospects of a satisfactory result is most desirable. It has been our experience that in the rubber tube such a factor is available.

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## **UROGENITAL ORGANS**



## TOXICITY OF PYELOGRAPHIC MEDIUMS: REPORT OF A DEATH FOLLOWING THE USE OF THORIUM NITRATE\*

E. H. WELD

There is no longer any question as to the value of pyelography. Whenever renal catheterization is necessary for diagnostic purposes the procedure is almost routine. Urologists have sought an opaque medium which would not be injurious, and all experimental work in the past has been done with the view of determining the effect of pyelographic mediums on the kidney tissue. It has been shown definitely that colloidal silver solutions are injurious to the kidney tissue and that they get into the circulation. I have recently shown that all pyelographic mediums and various dyes are rapidly absorbed from the kidney pelvis. The striking clinical results that are often obtained in cases of pyelonephritis by pelvic lavage with silver nitrate solutions have been explained as due to the action of the silver solution not only by its local effect on the kidney pelvis but also by its permeation of the kidney tubules (Braasch). In view of the work we have done in demonstrating that substances are absorbed from the tubules of the medullary portion, it seems plausible that such an explanation of the action of silver nitrate is correct. A recent death following pyelography for which a solution of thorium nitrate was used led us to make a study of the toxicity of the different pyelographic mediums.

### REPORT OF A CASE

Case 64235. A woman, aged 55, who was examined at the Mayo Clinic, Feb. 27, 1919, died following a urethral catheterization in which thorium nitrate was used as the pyelographic medium. The patient first came to the clinic in February, 1912, at which time she complained of pain with epigastric distress, rather typical of gallbladder disease. A cholecystostomy was performed and a chronic catarrhal cholecystitis

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(strawberry gallbladder) with a large number of stones was found. Recovery was uneventful and the patient was in good health until three months before her last examination; she then began to have attacks of epigastric distress coming on at night every two weeks, a dull severe ache with a sensation of fullness at the right costal border which would last two or three hours. She complained of some indefinite urinary symptoms. The examination of the urine showed it to be practically normal. The hemoglobin was 77 per cent; x-ray examination of kidneys, ureters, and bladder was negative.

The patient was given a cystoscopic examination in order to identify the source of the abdominal pain. A slight irritability of the bladder with a few areas of chronic inflammation, particularly at the right and left base of the bladder, was noted. Both ureters were of normal length and the secretion was clear. A specimen showed a moderate number of red blood cells. A differential functional test showed 17 per cent on the right and 12 per cent on the left with a return flow from the bladder of 2 per cent. Because of the right-sided pain, a pyelogram was made. Thorium nitrate, prepared by a well known pharmaceutical company, was the opaque medium used and was carefully injected. The patient did not complain of pain, she was somewhat weak and faint for a short time after getting off the table, but was able to go to her hotel. At the end of six hours she was suddenly seized with nausea, vertigo, and weakness. The symptoms became rapidly worse, with pronounced vomiting, and prostration, and she died at 7 p. m., nine hours after the pyelogram was made. The clinical diagnosis was negative so far as a pathologic condition in the kidney was concerned. The nature of her death suggested acute toxemia, evidently the result of pyelography.

At necropsy marked general arterial sclerosis, moderate fibrosis, fatty myocarditis, arteriosclerotic atrophy of the kidney, slight traumatic(?) hemorrhage in the pelvis of the right kidney, slight catheterization bruising of the urethra and ureteral mouths, marked edema of both lungs, small hypernephroma of the right adrenal gland about 2 cm. in diameter, right apical fibrous adhesive pleuritis, old atrophic cholecystostomy scar of the abdomen, moderate arteriosclerotic deformity of the gallbladder, fibrous adhesions between the gallbladder, parietal peritoneum, hepatic flexure of the colon, first portion of the duodenum, and the under surface of the liver, marked parenchymatous fatty changes in the liver, slight hyperplasia of the spleen, and petech-

ial hemorrhages in the mucous lining of the greater antrum of the stomach were found. Microscopic examination of the kidney showed some cloudiness of the tubular epithelium, with areas of acute congestion.

The stock of thorium nitrate solution on hand at the time was at once sent to the manufacturer, but unfortunately none was saved to be tested physiologically in our own laboratories. Several specimens of thorium nitrate solution of different ages were tested, however, and these showed varying toxicity.

### PHYSIOLOGIC TESTS OF THE TOXICITY OF THE MEDIUMS

Dogs were anesthetized and kept under light constant ether tension by the Connell apparatus. The carotid artery was arranged to record carotid blood pressure (mercury manometer). The femoral vein was exposed so that injections could be made easily either by syringe or burette. A 25 per cent solution of sodium bromid, a 25 per cent solution of potassium iodid, a 25 per cent solution of sodium iodid, and a 15 per cent solution of thorium nitrate were tested. The intravenous injection of sodium bromid in four different dogs produced practically no effect, even when 55 c.c. were given. Usually there was a slight increase in blood pressure, possibly due to an increase in the fluid volume. The injection of 2 or 3 c.c. of a 25 per cent solution potassium iodid caused the blood pressure to drop to zero, and almost instant death. When 50 c.c. of a 25 per cent solution of sodium iodid were used in two experiments, a very slight reaction followed from which the animal soon recovered. The toxicity of the 15 per cent solutions of thorium nitrate seemed to vary with the different ages of the solutions. Twenty-two cubic centimeters from Bottle A caused the death of the animal. Ten cubic centimeters from Bottle B caused a decided reaction noted in the blood pressure curve. One hundred cubic centimeters from Bottle C produced no apparent reaction. Fifty cubic centimeters from Bottle D caused the death of the animal. Forty cubic centimeters from Bottle E caused death, as did also 25 c.c. from Bottle E, when the solution was given to a slightly smaller animal. The contents of Bottle A was approximately one year old, of Bottle B approximately two months; Bottles C, D and E had just been received from the manufacturers.

Potassium iodid should be used with great care as a pyelographic

medium because of its toxicity and because of the fact that it is readily absorbed from the kidney pelvis. Death following the use of potassium iodid is very evidently due to the potassium radicle, since sodium iodid produces very little effect.

At least one of the toxic effects of thorium nitrate is on the heart muscle, as may be shown by the fact that cardiac failure follows the administration of thorium nitrate even after section of the vagi and the administration of such drugs as nicotin and atropin. Thorium nitrate seems to vary in toxicity according to the age of the solution, possibly because of the conditions under which it is kept.

Unfortunately, sodium or potassium iodid, in a solution of 20 to 25 per cent as originally recommended,<sup>1</sup> often causes considerable local irritation when used in the renal pelvis and bladder in man.

Sodium bromid is non-toxic, cheap, easily prepared, readily accessible, non-irritating, and would seem to be the best medium yet brought forward. We advise a 20 per cent solution for pyelography; a 10 or 15 per cent solution is sufficient for cystography. The drug should be chemically pure, and the solution should be sterilized by boiling before it is used.

#### PROTOCOLS

Experiment 300, Dog D124, April 22, 1919. A dog weighing 5 kg. was prepared in the usual manner. In one and-one-fourth minutes 1 c.c. of a 25 per cent solution of sodium bromid was injected into the right femoral vein; the pulse rate remained practically unaffected but the blood pressure was raised about 3 mm.

After allowing forty-five minutes for the dog to recover, 1 c.c. of a 25 per cent solution of potassium iodid was injected in one and one-fourth minutes. A decided reaction, probably toxic, followed.

The dog was allowed forty-five minutes in which to recover and 1 c.c. of a 15 per cent solution of thorium nitrate was injected which caused a slight irregular pulse curve. The solution, approximately one year old, came from Bottle A.

After eighteen minutes, 5 c.c. of thorium nitrate were injected in two and one-half minutes; this caused a rise in blood pressure of about 30 mm., which gradually decreased for three minutes, and then the blood pressure seemed to remain normal. The solution came from Bottle A.

Again after eighteen minutes 5 c.c. of a 25 per cent solution of

sodium bromid were injected which caused a very slight rise of blood pressure, and after another eighteen minutes 2 c.c. of a 25 per cent solution of potassium iodid were injected into the femoral vein. This caused a rapid fall in blood pressure and the death of the animal.

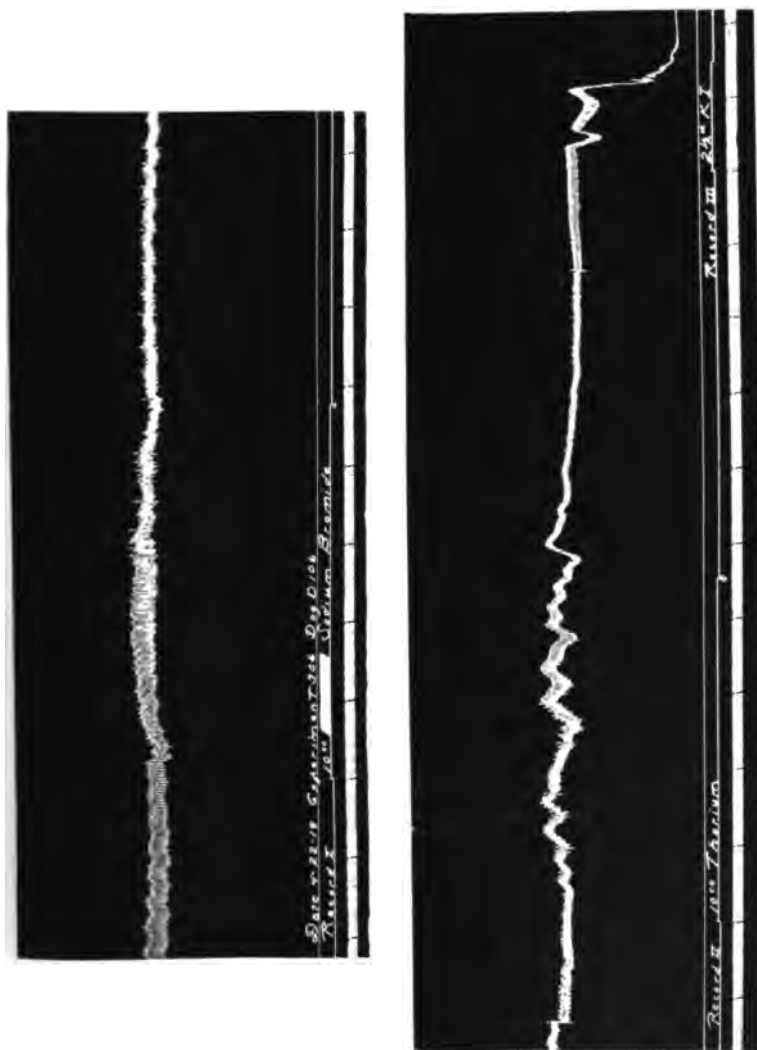


FIG. 92.—Record 1, the injection of 10 c.c. of 25 per cent solution sodium bromid. Record 2, the injection of 10 c.c. of 15 per cent solution thorium nitrate. Record 3, the injection of 2.5 c.c. of 25 per cent solution potassium iodid causing death. (Experiment 306, Dog D106.)

Experiment 306, Dog D106, April 22, 1919. A dog weighing 4.5 kg. was injected with 10 c.c. of a 25 per cent solution of potassium iodid into the right femoral vein at the rate of 2 c.c. a minute. The

blood pressure rose 6 mm. and the pulse curve was increased slightly in amplitude. After the completion of the injection the blood pressure returned to normal.



FIG. 93.—Record 4, the injection of 5 c.c. of 15 per cent solution thorium nitrate in the vein. Record 5, the injection of 5 c.c. of 25 per cent solution sodium bromid in the vein. Record 6, the injection of 2 c.c. of 25 per cent solution potassium iodid in the vein (Experiment 306, dog D106.)



FIG. 94.—Death of a dog following the injection of 22 c.c. of a 15 per cent solution of thorium nitrate (Experiment 311, Dog D131).

The animal was allowed forty-five minutes in which to recover when 10 c.c. of thorium nitrate were injected at the rate of 2 c.c. a minute. This gave a decided toxic curve and a slight rise in blood pressure, after which the curve returned to normal. The solution, approximately two months old, was taken from Bottle B.

After fifteen minutes the injection of 2.5 c.c. of a 25 per cent solution of potassium iodid at the rate of 2 c.c. a minute caused the immediate death of the animal (Figs. 92 and 93).

Experiment 311, Dog D131, April 23, 1919. A dog weighing 4.9 kg. was injected with a 15 per cent solution of thorium nitrate allowed to flow by gravity from a burette into the right femoral vein. For the first three minutes the rate was 1 c.c. a minute; 5 c.c. had entered in four minutes, 8 c.c. in six minutes, 10 c.c. in eight minutes, 16 c.c. in nine minutes, 20 c.c. in ten minutes, 22 c.c. in eleven minutes, at which time the animal died. It is probable that the animal would have died if a smaller quantity had been used. The solution, approximately one year old, came from Bottle A (Fig. 94).

Experiment 312, Dog D132, April 23, 1919. A dog weighing 4.7 kg. was injected with a 25 per cent solution of sodium bromid allowed to flow slowly from a burette into the right femoral vein at the rates noted in the preceding experiment. Thirty cubic centimeters were injected in thirteen minutes without causing any marked reaction. The blood pressure rose slightly, and the pulse seemed to increase in volume. The animal was allowed to remain on the table thirty minutes, and another record was taken (Fig. 95).

Experiment 314, Dog C268, April 24, 1919. A dog weighing 12 kg. was injected with a 15 per cent solution of thorium nitrate, allowed to flow gradually from a burette into the left femoral vein. Six cubic centimeters had entered in five minutes, 10 c.c. in eight minutes, 30 c.c. in thirteen minutes, 50 c.c. in eighteen and one-half minutes. Following this the animal was given one hour in which to recover when 50 c.c. more were allowed to flow into the vein in thirteen minutes. This injection did not seem to have any toxic effect on the dog. The solution, approximately one month old, came from Bottle C which had recently been received from the manufacturer.

Experiment 316, Dog D135, April 28, 1919. A dog weighing 7.2 kg. was injected with a 25 per cent solution of sodium bromid allowed to run by gravity from a burette into the left femoral vein at the rate of 3 c.c. in three minutes, 6 c.c. in eight minutes, and 55 c.c. in eleven minutes. This produced no ill effect. There was a slight rise in blood pressure which gradually returned to normal after the injection had been discontinued. The animal was killed by injecting 2.5 c.c. of 15 per cent colloidal silver solution directly into the vein.

Experiment 317, Dog D136, April 28, 1919. A dog weighing 10.4



FIG. 95.—The injection of 30 c.c. of 25 per cent solution of sodium bromid (Experiment 312, Dog D132).



FIG. 96.—Death of a dog following the injection of 50 c.c. of thorium nitrate solution (Experiment 317, Dog D136).

kg. was injected with thorium nitrate allowed to run by gravity from a burette into the left femoral vein. In the first minute 6 c.c. were injected, causing a rapid fall in blood pressure. The animal was allowed one minute in which to recover. At the end of three minutes 9 c.c. had been injected, in four minutes 12 c.c., in five minutes 14 c.c., in six minutes 17 c.c., in seven minutes 21 c.c., in eight minutes 32 c.c., in nine minutes 37 c.c., in ten minutes 41 c.c., in eleven minutes 44 c.c., in twelve minutes 47 c.c., in thirteen minutes 50 c.c. The solution was then injected at the approximate rate of 4 c.c. a minute. At the end of eight minutes the blood pressure gradually began to drop, and continued to fall until 50 c.c. had been injected when the animal died. The solution was taken from a bottle (Bottle D) which had been received from the manufacturer about one week before. The bottle had not been opened until it was used in this experiment (Fig. 96).

Experiment 319, Dog D138, April 29, 1919. A dog weighing 9 kg. was injected with thorium nitrate solution allowed to flow from



FIG. 97.—Death following the injection of 40 c.c. of thorium nitrate solution (Experiment 319, Dog D138).

a burette into the left femoral vein. In one minute 4 c.c. were injected, in two minutes 10 c.c., in three minutes 15 c.c., in four minutes 20 c.c., in five minutes 25 c.c., in six minutes 30 c.c., in seven minutes 34 c.c., in eight minutes 38 c.c., in eight and one-half minutes 40 c.c, at which time the animal died. The blood pressure had risen gradually until 30 c.c. had been given, and then it began to sink in a more rapid curve than that in which it had risen until death ensued three minutes later. The solution, which had not been used until this experiment, was taken from Bottle E (Fig. 97).

Experiment 321, Dog D140, April 30, 1919. A dog weighing 5.2 kg. was injected from a burette arranged to allow a 25 per cent



solution of sodium iodid to flow into the right femoral vein. In one minute 3 c.c. were injected, in two minutes 6 c.c., in three minutes 9 c.c., in four minutes 13 c.c., in five minutes 17 c.c., in six minutes 20 c.c., in eight minutes 25 c.c., in nine minutes 30 c.c. The curve was somewhat irregular at this time due to very light anesthesia. In ten minutes 33 c.c. were injected, in eleven minutes 40 c.c. The animal struggled somewhat, due to light anesthesia. In thirteen minutes 44 c.c. were injected, in fourteen minutes 50 c.c. There was apparently very little toxic effect. The animal was given 2 c.c. potassium iodid which caused instant death, apparently from heart failure.

Experiment 327, Dog D141, May 1, 1919. A dog weighing 5.4 kg. was injected with a 25 per cent solution of sodium iodid allowed to flow from a burette into the right femoral vein. In one minute 1.5 c.c. were injected, in two minutes 4.5 c.c., in three minutes 8 c.c., in four

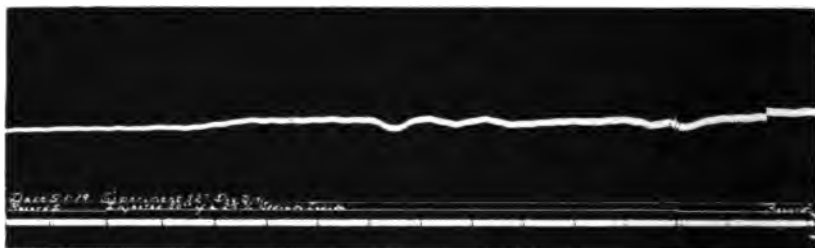


FIG. 98.—The injection of 50 c.c. of a 25 per cent solution of sodium iodid (Experiment 327, Dog D141).

minutes 11 c.c., in five minutes 16 c.c. At this time there was a slight fall in blood pressure because of the too rapid injection. In six minutes 21 c.c. were injected, in seven minutes 24 c.c., in eight minutes 31 c.c. The blood pressure fell again because of too rapid injection. In nine minutes 35 c.c. were injected, in ten minutes 43 c.c., in eleven minutes 50 c.c. The record was stopped; after fifteen minutes it was run for a short interval showing that the blood pressure had risen about 20 mm. above the original. From this experiment it would seem that sodium iodid is non-toxic, but when given rapidly intravenously causes a slight reaction (Fig. 98).

Experiment 335, Dog D144, May 6, 1919. A dog weighing 5.8 kg. with blood pressure of 150 mm. was injected with 15 c.c. of a 15 per cent thorium nitrate solution taken from Bottle E and

allowed to flow from a burette into the femoral vein at the rate of 3 c.c. a minute. The blood pressure gradually rose until it reached 200 mm. at the end of five minutes when it began to fall slightly; the



FIG. 99.—Record 1, the injection of 15 c.c. of a 15 per cent solution of thorium nitrate. The injection was stopped at "A" and animal allowed to recover. The rate of injection was 3 c.c. per minute. Record 2, the injection of 10 c.c. of a 15 per cent solution of thorium nitrate in one and one-fourth minutes causing rapid fall in blood pressure and finally death of the dog (Experiment 335, Dog D144).

injection was, therefore, discontinued. The pulse became very slow and full, increasing to a large pulse pressure after the injection was stopped. The blood pressure in the meantime rose to 230 mm. Two minutes after the injection was stopped the blood pressure gradually began to fall and at the end of forty-five minutes it had dropped to 110 mm.; at this time Record 2 was taken. Ten cubic centimeters of a 15 per cent solution thorium nitrate were then injected in one and one-fourth minutes. This caused a rapid rise in blood pressure up to 165 mm. in one minute. The blood pressure began to fall, the heart became very slow, but recovered and the record was continued for twenty minutes and showed the gradual fall of the blood pressure, while the pulse pressure was large and the pulse very slow and full. As it was evident at the end of twenty minutes that the animal would die, the vagi were sectioned. This had no effect on the pulse or blood pressure, proving that the toxic effect was not on the central nervous system (Record 3, Signal C). Nicotin injected intravenously produced no effect; this showed that the effect of the drug was not on the nerve ganglion. Atropin was injected and produced no effect, demonstrating that the action was not on the nerve endings. The animal would probably have been killed at the first injection if more than 15 c.c. had been given. The action of the drug is directly on the heart, particularly when a large dose is given rapidly (Fig. 99).

#### PHYSIOLOGIC TESTS OF THE TOXICITY OF PYELOGRAPHIC MEDIUMS

Experiment	25 per cent sodium bromid		Bottle	15 per cent thorium nitrate		25 per cent potassium iodid		25 per cent sodium iodid	
	Amount	Reaction		Amount	Reaction	Amount	Reaction	Amount	Reaction
300	1 c.c.	None	A	1 c.c.	None	1 c.c.	Toxic		
300	5 c.c.	None	A	5 c.c.	Slight	2 c.c.	Death		
306	10 c.c.	None	B	10 c.c.	Toxic	2 ½ c.c.	Death		
311	.....	.....	A	22 c.c.	Death				
312	30 c.c.	None							
314	.....	.....	C	100 c.c.	None				
316	55 c.c.	None							
317	.....	.....	D	50 c.c.	Death				
319	.....	.....	E	40 c.c.	Death				
321	.....	.....						50 c.c.	None
327	.....	.....						50 c.c.	Very slight
335	.....	.....	E	25 c.c.	Death				

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## THE PELVIS OF THE KIDNEY AS A POSSIBLE SOURCE FOR INFECTION OF THE BLOOD STREAM: A PRELIMINARY REPORT\*

J. A. H. MAGOUN, JR.

During recent years it has been generally conceded that in cases of renal infection the kidney is infected secondarily following a primary bacteremia. In some instances it seems that the kidney, previously infected either through the blood stream or by an ascending infection, may be the cause from which a bacteremia results. For the purpose of investigating this interesting problem, experiments have been conducted under the direction of the Departments of Urology, of Experimental Bacteriology, and of Experimental Surgery, with reference to the following questions:

1. Can organisms pass from the pelvis of the kidney into the blood stream?
2. Are the conditions under which they pass at all analogous to the pathologic status found clinically?
3. Are there clinical cases in which the kidney has acted as a focus of infection?

Our investigations have been concerned, as yet, only with the first two of these hypothetic questions.

The literature concerning the absorption from or the passage of organisms through the kidney is very meager. Albarran was the first to investigate experimentally the infections of the blood stream through the kidney. In 1888, working with the *Bacillus pyogenes*, which was afterwards identified as the *Bacillus coli* by Krogius, Achard and Renault, he produced infection in the blood stream by introducing the organism into the ureter. His work was without previous bacteriologic control of the blood, however, and in many cases peritonitis occurred. He traced the organism from the bladder to

\* Reprinted from Jour. Am. Med. Assn., 1920, lxxiv, 73-75.

foci of infection in the kidney; "from these foci the organisms go into the connective tissue and then penetrate into the blood vessels, enter the circulation, and lead to far off emboli." Thus it is seen that thirty years ago the thought was suggested that the kidney might be a focus for blood stream infection.

Burns and Schwartz do not believe that absorption takes place from the pelvis of the kidney under normal conditions. If an acute pyelitis occurs, however, absorption and the clinical phenomena of chills and fever result. These authors consider such clinical manifestations due to the absorption of urine and bacterial toxin either from the blood vessels or lymphatics of the renal pelvic mucosa directly, or from the urine and bacterial toxins retained in the uriniferous tubules. They do not suggest, however, that these clinical symptoms may be due to the passage of the bacteria through the kidney into the blood stream, thus causing a bacteremia. In their later work, after the injection, by the gravity or syringe method, of indigo carmin and india ink particles into the previously ligated ureter, they found these substances in the opposite kidney, in the liver, lungs, and spleen. They then conclude: "It is reasonable to suppose that if particles of ink can travel in this manner, bacteria and other foreign substances can do likewise."

Macht states that certain drugs or poisons may be absorbed through the walls of the ureter and the kidney pelvis. Weld has shown with what ease certain drugs may be absorbed from the renal pelvis, and the untoward action of some of them. Weld's finding that "absorption from the kidney pelvis indicates that the kidney may be a focus of infection which should always be considered," stimulated me to make the present investigation.

#### EXPERIMENTAL WORK

Dogs were used in all the experiments. The animals were etherized with a constant ether tension; their condition was kept as near normal as possible by the judicious use of heat, and so forth. In some of the experiments the blood pressure was recorded. All operative manipulations were carried out with the minimum of trauma and hemorrhage. *Bacillus prodigiosus* was the organism chosen since it is easily identified, since it probably never occurs spontaneously in the sites cultured, and since it is rarely the cause of bacterial contamination

in the laboratory. The bacillus was grown in broth cultures and injected by the gravity method.

A straight glass tube about 2.5 mm. in diameter was connected by a T-tube to a cannula inserted into the ureter and to a graduated burette. The straight glass tube was graduated in cubic millimeters. A stop cock was inserted on each side of the T-tube. The fluid containing the bacteria was placed in the burette and allowed to flow into the graduated tube to any desired height. At this definite and controlled pressure it was then allowed to enter the ureter. Great care was taken to exclude air from the entire system and not to contaminate adjacent tissues.

The dogs were killed with ether at the end of from two to three hours and cultures taken from the heart's blood, the lungs, liver, spleen, inferior vena cava opposite the renal vein, right kidney cortex and medulla, and left kidney cortex and medulla. The cultures were made by planting from 2 c.c. to 5 c.c. of blood and from 0.2 c.c. to 0.5 c.c. of the tissue juice of the various organs into tall tubes of glucose broth. The material from the tissues was obtained by aspirating the macerated particles and juice into sterile pipettes. The inoculated tubes were allowed to stand at room temperature for from forty-eight to ninety-six hours. The positive cultures were then plated on plain agar.

*Series 1.*—In the first series through a lumbar incision a cannula was inserted into the left ureter from 2 cm. to 4 cm. from the pelvis of the kidney. A twenty-four hour broth culture of *Bacillus prodigiosus* was then permitted to flow into the pelvis at from 10 cm. to 30 cm. pressure. From two to three hours afterward the dogs were killed with ether and cultures made as outlined above. Results are shown in Table 1. In 12 experiments even with this low pressure *Bacillus prodigiosus* was recovered from the blood stream or other organs in three instances. It was found in the left kidney in all but two of the experiments.

*Series 2.*—The procedure in the second series was the same as in the first, with the exception that the pressure at which the organisms were passed into the ureter was increased to from 60 cm. to 78 cm. Results are shown in Table 2. At this pressure, which was slightly less than the secretory pressure of the kidney, the organisms were recovered from the blood stream or other organs in six of seven experiments, and they were recovered from the left kidney in all.

*Series 3.*—In the third series in addition to the procedure followed in Series 1 and 2 a cannula was inserted into the right ureter 4 cm. above the bladder; to the cannula was attached a straight glass tube. The cannula inserted into the left ureter was also 4 cm. above the bladder. A forty-eight hour broth culture of *Bacillus prodigiosus* and washings from forty-eight hour agar slants were placed in the burette and allowed to flow into the left ureter, while the pressure was kept under 21 cm. The tubing connected with the cannula in the left ureter was then clamped. The femoral vein was isolated and from 100 c.c. to 150 c.c. of a 5 per cent sodium sulphate solution were injected slowly. The secretory pressure of the right kidney was measured in the graduated tube connected with the right ureter. After two to three hours the routine procedure as previously described was carried out. The organisms were introduced under a very low pressure and the intrapelvic pressure was subsequently increased by stimulation of the kidney. The results are shown in Table 3. In four of these five experiments *Bacillus prodigiosus* was recovered in other organs than the kidney.

It may be concluded, therefore, that bacteria can pass from the kidney pelvis into the blood stream and that they may do this under conditions analogous to some of the pathologic states found in man.

TABLE 1.—RESULTS OF EXPERIMENTS IN SERIES 1

Experiment	Pressure above kidney pelvis cm. of water	Positive cultures <i>Bacillus prodigiosus</i>
550-19	20 to 30	1. Renal vein 2. Left kidney cortex 3. Left kidney medulla
560-19	20 to 30	1. Left kidney medulla
562-19	20 to 30	1. Left kidney cortex 2. Left kidney medulla
565-19	10 to 30	1. Heart blood 2. Liver 3. Renal vein A and B
592-19	20 to 30	All cultures negative
618-19	20 to 30	1. Left kidney cortex
620-19	20 to 30	1. Left kidney cortex
630-19	20 to 30	1. Left kidney cortex 2. Right kidney cortex
649-19	20 to 30	1. Left kidney cortex
654-19	20 to 30	1. Left kidney cortex
657-19	20 to 30	1. Left kidney cortex
666-19	20 to 30	All cultures negative

TABLE 2.—RESULTS OF EXPERIMENTS IN SERIES 2

Experiment	Pressure above kidney pelvis cm. of water	Positive cultures <i>Bacillus prodigiosus</i>
531-19	78	1. Left kidney cortex 2. Left kidney medulla
534-19	70	1. Heart blood 2. Right kidney 3. Liver 4. Renal vein?
704-19	60	1. Lung 2. Renal vein <i>A</i> and <i>B</i> 3. Heart blood <i>A</i> and <i>C</i> 4. Right kidney cortex 5. Left kidney cortex 6. Right kidney medulla 7. Liver <i>A</i> and <i>B</i> 8. Spleen
800-19	60	1. Renal vein 2. Left kidney cortex
801-19	60	1. Liver <i>A</i> and <i>B</i> 2. Renal vein <i>A</i> , <i>B</i> , and <i>C</i> 3. Heart blood <i>A</i> , <i>B</i> , and <i>C</i> 4. Spleen 5. Right kidney cortex
802-19	60	1. Liver <i>A</i> and <i>B</i> 2. Spleen
803-19	78	1. Heart blood <i>A</i> , <i>B</i> , and <i>C</i> 2. Renal vein 1 and 2 3. Liver 1 and 2 4. Left kidney cortex

TABLE 3.—RESULTS OF EXPERIMENTS IN SERIES 3

Experiment	Pressure in left ureter cm. of water	Pressure in right ureter cm. of water	Positive cultures <i>Bacillus prodigiosus</i>
739-19	20	65	1. Lung 2. Heart blood <i>A</i> , <i>B</i> , and <i>C</i> 3. Renal vein <i>A</i> and <i>B</i> 4. Liver 5. Right kidney cortex 6. Left kidney cortex
756-19	20	64	1. Renal vein 2. Liver 3. Left kidney cortex
760-19	20	78	1. Liver 2. Left kidney cortex
804-19	20	50	1. Heart blood 2. Left kidney cortex
805-19	20	65	All cultures negative



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## HEMATOGENOUS INFECTIONS OF THE KIDNEY\*

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The surgical aspects of nephritis have led to extensive discussion, and but little agreement exists with regard to the types that are not clearly surgical. Wide differences of opinion are also manifest among those who have given the most time and attention to the study of nephritis in general. The accumulated literature on the subject is monumental; much of it, unfortunately, is confusing, and often even the fundamentals are the subject of controversy. Recently, however, articles have been published that help to clear up some of the moot questions.

Historically, the chief point of interest with reference to nephritis is the profound knowledge of the various phases of the disease exhibited by Richard Bright, one of a long line of brilliant workers in Guy's Hospital, London. In 1827 and again in 1836 Bright, in epoch marking papers on edema and on albuminuria, pointed out that fundamentally there are two kinds of nephritis: Type 1, the acute or "wet" nephritis; and Type 2, the chronic or "dry" nephritis.

Type 1, which involves the kidney filter, was to be recognized pathologically in cases in which the large white kidney was found. Clinically, the type was characterized by edema, especially in the acute stage, and by urine containing albumin and casts, and at times blood corpuscles, the urinary findings varying in extent with the acuteness of the process and the amount of involvement of the kidneys. Both kidneys are always involved and exhibit a wide pathologic architecture. The morphology varies as the toxic agents vary in toxicity and affect different structures of the kidney.

*Bright's Type 1 nephritis.*—Since the publication of Bright's work, we have learned that Type 1, or the "wet" type of nephritis, is usually the result of toxins developed in the course of infectious diseases.

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Diphtheria antitoxin affords the best known example of the effect of bacterial toxins on the kidney; it may produce changes in the kidney analogous to the nephritis which sometimes develops in cases of diphtheria. The frequency with which Bright's Type 1 and infective nephritis follow lesions of the skin and mucous membrane, especially in children, is worthy of note, as shown by the nephritides following scarlet fever, tonsillitis and so forth. In the adult, exposure to cold, especially of the cutaneous surfaces, plays a definite rôle. The value of the skin as an aid to elimination in cases of defective kidney function has long been well known. The effect produced by hot packs and similar therapeutic measures is to cause a flow of perspiration which may eliminate large amounts of chlorids and some urea.

It is true that acute nephritis may be produced by other toxic agents, such as cantharides, but to all intents and purposes an infection lies behind it. The edema is to a large extent due to a failure of elimination of chlorids. Chlorids, usually taken in the form of common salt, are a constant requirement of all animal life. The herbivorous and omnivorous animals obtain the necessary amount in the form of salt, while the carnivorous obtain a sufficient amount from the flesh which they consume. The chlorids are largely excreted by the kidneys. In acute nephritis, chlorid is not fully eliminated, and edema results. The physical and chemical reactions involved in the production of edema by chlorid retention are still greatly disputed, however, and it is apparent that varying factors are to be considered.

*Bright's Type 2 nephritis.*—Bright's Type 2, called the dry type because edema is not present, involves the connective tissue and blood vessels, especially the arteries; the patient suffers from headache, nausea, vomiting, hypertension, and other symptoms of uremia. The symptoms may be latent for long periods. Urea retention is one of the final consequences of this type. While urea will not of itself, when in excess in the blood, produce uremia, it is closely associated with if not one of the agents which produce the uremic manifestations. Both kidneys are involved, and pathologically in the typical case the kidneys are contracted and granular. The urine is of low specific gravity, pale, and large in amount. The urinary findings may consist only of an occasional cast and a trace of albumin, although at times there may be large amounts of albumin. This type of Bright's disease is closely associated with or is a part of a general vascular disease, and perhaps should not be described as a true primary nephri-

tis. Changes in the heart are so characteristic of chronic Bright's disease that the appellation of cardiorenal disease is at times not inappropriate. The pathologic architecture varies with the situation of the chief connective tissue deposits and the changes in the renal vascular system. Bissell and other pathologists call attention to the fact that many of the changes in the kidney called nephritis are regressive in character. Neither infections nor the products of infection, so far as is known, play an important part in the etiology of Bright's Type 2. The cause of the condition is as yet unknown, but it is probably due to disorders of metabolism.

Edema may develop in chronic Bright's disease (Type 2), but if it does it is almost invariably the result of cardiac failure and not of salt retention. Widal had divided nephritis functionally into two forms: the chloremic or salt retention type, corresponding to Bright's Type 1, and the azotemic, nitrogen, or urea retention type, corresponding to Bright's Type 2. It has been asserted by various authorities that chronic Bright's Type 2 is the late result of Type 1. I am convinced, however, that Bright's Types 1 and 2 are entirely independent diseases.

A discussion of the differentiation is unnecessary here, but the confusion seems to arise from mixed types. In certain varieties of Bright's Type 1, chronicity may be a feature. This is especially true of a form of Type 1, caused by chronic focal infections. I have seen what were believed to be cases of Bright's Type 1, caused by chronic infections of the teeth, tonsils, gallbladder, or by duodenal ulcer, and so forth. The patients recovered from the nephritic disturbance after operative cure of the focus of infection. Subacute infections, with slowly sterilizing abscesses, often cause symptoms of a nephritis which disappears as the cause is removed. Excessive connective tissue may develop in the kidneys in some cases of Type 1 so that they closely resemble the contracted kidneys of Type 2; but the vascular changes are different. Again, chronic Bright's disease, Type 2, acts as a cause for lowered resistance of the kidneys, and a secondary true nephritis of Type 1 may be added to the condition, especially as a terminal infection leading to the frequent postmortem finding of death from acute nephritis superimposed on chronic nephritis. This confusion is further increased in some cases by pathologic changes in the kidney, the late results of unrecognized hematogenous infection which might well be called Type 3.

*Function of the kidney.*—Rowntree calls attention to the fact that medicine of the last decade centers around the question of function, so far as the kidney is concerned. The capacity of the kidney to carry on its work, rather than its appearance, has come to be recognized as the important factor. This is well shown by the value clinically of the phenolsulphonaphthalein test and the test of the chemistry of the blood. The percentage of urea in the blood or the phenolsulphonaphthalein test will frequently give a clue to the state of the kidneys that cannot be obtained from the urinary findings.

That the kidney in health filters bacteria out of the blood, and by so doing receives no injury, is a fact too well known to require comment. It is the retention of the bacteria in the kidney which produces the trouble. But we know much less about its ability to filter out toxic materials. In the greater number of cases of nephritis no bacteria are found, and we must believe that it is some material, the result of infection, rather than the bacteria themselves that cause the trouble, although it is possible that an ultramicroscopic organism exists as the causative factor. The kidney normally filters out urea, which is the ash of protein derivatives, the amino-acids. The patient with a granular, contracted kidney (Bright's Type 2) must of necessity pass a large quantity of urine; the specific gravity is low because the kidney filter is damaged and fails to eliminate normal concentrations of urea and similar bodies. As these products are not threshold bodies, they are always to be found in both the blood and the urine.

On the contrary, sugar in the blood is a threshold body. When it rises beyond the normal, the excess flows off through the urine, and diabetes results. The threshold, however, is not an exact point, and many persons with crops of boils or carbuncles may, by testing the blood for sugar percentages, be shown to have an increased amount of blood sugar without having sugar in the urine, just as in others a low threshold permits the escape of sugar from slight temporary causes, so-called dietetic or alimentary glycosuria, which is without pathologic significance.

Embryologically, the kidney has a double origin: First, the ureter, pelvis, calices, and straight collecting tubules, all lined with pavement epithelium, which are derived from the wolffian duct and have no function beyond that of collecting urine as it is formed. The chief response of the part of the kidney thus derived, when diseased, consists in the development of infections, calculi, and so forth, and if

the disease is a malignant, it is a true carcinoma. Obstructions to the urinary outflow at any point are most potential of mischief through failure of drainage. The medullary part of the kidney is composed of the urinary collecting channels just described and of the venous channels which carry back the purified blood to the general circulation. Second, the filtering portion of the kidney, which arises from the mesothelium and forms in large part the cortical substance which is the arterial portion of the kidney, bringing blood from the general circulation for purification. The common, solid tumors of the kidney that we have miscalled hypernephroma are, as pointed out by Wilson true mesotheliomas; that is, malignant neoplasms arising in the kidney filter. I think we may agree with Cushny that the kidney does not secrete urine, but filters it. The kidney may be aptly compared with a separator. The arterial blood enters the kidney cortex, the urine is filtered out, and the venous blood passes back to the general circulation. Weld, by his experimental injections of mediums, demonstrated the physics of the process outlined. The partial failure of the two halves of the kidneys to unite, so that the urine, when filtered, is not freely admitted into the collecting tubules, produces the so-called congenital polycystic kidneys that are eventually associated with chronic nephritis.

*Type 3 nephritis.*—Nephritis, the result of living organisms, may be called Type 3. True nephritis is concerned with the filter portion of the kidney, and the failure to filter out all the bacteria and their retention is responsible for the occurrence of one form of the disease, which is of great surgical importance. As to just how often such infections may be ascending or lymphogenous rather than hematogenous in origin there is a diversity of opinion. My own opinion is that such infections, other than hematogenous, are extremely rare so far as the kidney filter is concerned, though it is possible they may be more frequent in that part of the kidney devoted to collecting urine.

Accepting the idea that there is a common form of true nephritis which differs from Bright's Types 1 and 2 and is caused by a bacterial infection, we quickly see that the effect on the kidney will depend on the nature of the bacteria, their number, and on the condition of the kidney itself, whether, for example, there is an anomaly present, such as hydronephrosis or calculi, which makes the kidney more vulnerable. The importance of this has been shown by Cabot and Crabtree, who demonstrated that the pus cocci affect the cortex of

the kidney and often follow lines of least resistance toward the periphery, and that the colon bacteria affect the straight collecting tubules of the pyramids, extend from them to the pelvis, and there produce a pyelitis. Pyogenic infections may lead to cortical abscesses and other evidences visible to the eye; but with scanty urinary findings beyond a trace of albumin and a few microscopic pus and blood cells, the urinary evidences are so slight in the acute stage, as to be overlooked unless great care is exercised. In the subacute and chronic forms the kidney may be more or less destroyed, and the common forms of pyonephrosis will follow. The pyogenic cocci are short lived and often are not to be found in the pathologic changes their action initiates. On the contrary, colon bacteria, by the production of copious, purulent sediment in the urine, give abundant evidence of infection without abscess formation in the kidney. Acute nephritis (Bright's Type 1) is the result of toxic products, not of living organisms, as in diphtherial and scarlatinal nephritis, and the two kidneys are equally involved. When the nephritis is the result of living bacteria (Type 3) the kidneys may be involved unequally or unilaterally, the unilateral infection being in the kidney which is more vulnerable because of some physical defect. The pus-producing organisms affect the kidney much as do tuberculosis bacilli, and those who have studied tuberculosis of the kidney will recognize the resemblance.

Hematogenous nephritis is often caused by cocci found in the skin, especially staphylococci from boils, carbuncles, and so forth, and from focal infections generally. The staphylococcus is short lived and often affects only one kidney. Acute streptococcal infections are most malignant. Subacute and chronic streptococcal infections occur commonly as a result of septic endocarditis, and appear in the kidney as a terminal infection, embolic in character.

In the fulminating type of hematogenous pyogenic infection, unless nephrectomy is performed, death may often result within a few days. The acute condition is often confused with acute intraperitoneal infections; on the right side, especially, is the differentiation from cholecystitis and appendicitis necessary. This may also be true of the less acute form. In the subacute and chronic forms, natural processes may localize and sterilize the foci of infection, and the patients may fully recover, or partial recovery may later be followed by chronic infection, and the kidney will be converted into a pyonephrosis. The fact should be recalled that septic infarcts rupturing

through the capsule of the kidney are the most common cause of perinephritic abscess.

Bright's disease, both Type 1 and Type 2, is of surgical interest only because of complications. But all the nephritides caused by living bacteria (Type 3) are of great surgical interest and have, until recently, been confused with Bright's disease. Hematogenous kidney infection is the one bright picture in a group of maladies that have been discouraging in the extreme. The surgeon of today is as greatly interested in nephritis as is the internist.

In reviewing the large mass of literature on nephritis, rather superficially, it is true, I have been particularly impressed with the clear and logical presentation made by Brewer in a series of published papers beginning in 1911, in which he demonstrates hematogenous pyogenic infections of the cortex of the kidney clinically, experimentally, and pathologically. In this connection, I wish to comment on the value of the contributions of the surgeon to such problems. Nephritis has been studied largely from a clinical and a postmortem standpoint. Clinical observations in these cases are notoriously unreliable, while the necropsy shows the terminal conditions that cause death. This exposition of terminal change, determined at necropsy, is exceedingly difficult to interpret in the living, and the final catastrophe leading to the death of the patient produces pathologic changes obscuring those that existed during life. In no other way can I explain the various theories and controversies which have marked the history of the study of nephritis. The clinician attempts, by study of the urine and the symptoms of the patient, to explain the terminal conditions found after death, which may not have existed at the time the clinical examinations were made. The surgeon, not by reason of greater acumen but by opportunity, now furnishes the missing link in the investigation which carries the truth, and makes possible an exact study of the kidney before the terminal infections, which are encountered at necropsy, obscure the picture.

Payne and MacNider and Buerger have shown the hematogenous origin of certain of the so-called chronic, essential hematurias, demonstrating that infection in and about the straight tubules, resulting in the development of scar tissue, which interferes with the venous circulation, causes congestion and varicosity of papillæ and leads to rupture and renal hemorrhage. This gives a pathologic explanation for several cases in which we explored to find the cause of renal hemor-



rhage, and in which one or more papillæ were found to be the seat of varicosities.

I have been greatly interested in the chronic form of hematogenous nephritis of bacterial origin. In a number of instances, I have explored and found small, cortical, pimple-like collections of fluid in the kidney in various stages of sterilization. I have been able to link up another most interesting sequel to the condition, namely, the occasional deposit of calcium carbonate in such an infected area, usually close to or connected with the capsule, which produces a roentgen-ray shadow resembling that of stone. The diagnosis of stone is often justified by the history of the acute, severe attack which marks the onset of infective nephritis. I have known such deposits of lime to form as soon as two months after the primary symptoms. Why in some persons, lime is deposited during the process of the cure of the infection, I do not know. The kidneys in such cases are often painful. Our patients were relieved by the excision of the lime masses, and by decapsulation. In several cases, the deposits of lime were deeper in the cortex. There are almost no urinary signs or symptoms in these cases, as the masses are in the cortex with little communication with the collecting parts of the kidney. It is very evident, too, that in some painful kidneys, with dense scars in the capsule, the origin is similar, and the condition may be relieved by decapsulation. I have been slow to admit that capsular compression of the kidney could be the cause of symptoms, but I have seen at least three cases in which hypertrophy of the remaining kidney within its fibrous capsule, after the removal of its fellow for disease, produced pain from the stretching of the capsule. The kidneys were low and movable, and the patients thin, and I was able to follow the compensatory hypertrophic enlargement by palpation, and to satisfy myself that the hypertrophy caused the pain.

In our experience, decapsulation has been valuable in this small group of cases in which there are scars and lime deposits in the capsule of the kidney, and in another group still more rare, that of acute nephritis (Bright's Type 1), in which, as pointed out by Morris, the operation occasionally enables the kidneys to functionate when urinary function has ceased and the patients are apparently in a dying condition. For movable kidney, and so forth, we have seen no good effect from nephrorrhaphy other than the psychic.

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## RECENT ADVANCE IN THE DIAGNOSIS OF SURGICAL LESIONS OF THE KIDNEY\*

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Recent advance in methods of diagnosis of surgical conditions of the kidney has been largely in the field of roentgenography and renal functional tests. Roentgenography of the urinary tract rendered opaque to the x-ray by injected mediums is now recognized as an indispensable factor in the diagnosis of surgical renal lesions. Its development was retarded during several years by the use of opaque mediums which caused injury to the injected kidney, namely, the salts of colloidal silver. This was largely overcome by the use of thorium as suggested by Burns. The occasional toxicity and the difficulty of preparation of this solution, however, prevented it from being an ideal medium. Although sodium iodid, as suggested by Cameron, obviated these objections, it remained for Weld to discover that ordinary sodium bromid has all the requisites of the ideal medium, since it is thoroughly soluble, non-irritating, non-toxic, easily prepared, and inexpensive. As a result, by using this inert medium, pyelography may be employed almost routinely with cystoscopy. There is scarcely a lesion in the urinary tract in which it has not proved of distinct diagnostic value. Since the interpretation of the pyelogram has been quite fully described in recent literature I shall not go into detail concerning the various deformities of the pelvic outline.

With the improvement and standardization of x-ray apparatus as well as operative technic, roentgenographic examination of the urinary tract has become so wide-spread that there are now but few surgeons who do not have access to this invaluable diagnostic aid. In the diagnosis of renal lithiasis much progress has been made in the interpretation of the numerous confusing shadows which appear in the roentgenograms of the urinary tract. Although many of these

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shadows may be identified by their contour, character, and position, a large number are impossible to interpret without the combined aid of clinical, laboratory, and cystoscopic data. The greatest accuracy, however, can be obtained only through the combined use of the cystoscope and roentgenographic technic, as employed in pyelography. The pyelographic data that will enable us to determine whether a doubtful shadow is extrarenal or intrarenal are as follows: (1) The distance separating the shadow from, (2) the exact relation of the shadow to, and (3) the presence of pathologic changes in the pelvic outline.

Shadows appearing in the area of the urinary tract which most frequently are responsible for error in interpretation are those caused by calcareous deposit in the extra-urinary tissue, gallstones, and tuberculous renal caseation. Such shadows may lead either to needless exploration of the urinary tract, or they may be erroneously regarded as extra-urinary.

It is well known that a gallstone is, as a rule, not visible in the roentgenogram. Nevertheless, as a result of the improvement in roentgenographic technic it is being found with such frequency as to warrant its consideration in the interpretation of every shadow in the right upper abdominal quadrant. The similarity of subjective symptomatology which not infrequently occurs between renal stone and gallstone may render the clinical data of little aid in interpreting such shadows. While the character of the gallstone shadow is distinctive and often is easily recognized, error in interpretation is easily possible. The greatest problem in the x-ray diagnosis of gallstone is to distinguish its shadow from that of renal stone. If the gallstone shadow is situated in the usual position of the kidney, and, should there be a coincidental infection of the urinary tract, the diagnosis may be exceedingly difficult. On the other hand, a renal stone may not infrequently be seen lying well above the twelfth or even the eleventh rib, in the usual gallbladder area. Furthermore, the renal stone may assume characteristics very similar to those of the gallstone. In short, the shadow in the roentgenogram cast by a gallstone and by a renal stone may be identical in position and character. The pyelogram is usually the best and frequently the only method by which the gallstone may be identified. The same data previously named in the identification of the extrarenal shadow are applicable in the differentiation of gallstones and renal stones.

*Renal tuberculosis.*—Recent literature has emphasized the importance of recognizing shadows caused by calcified areas in a tuberculous kidney. Although they can frequently be identified by their characteristic shadow, the combined clinical and cystoscopic data may be necessary for their recognition. The shadows are of three types, namely (1) small scattered areas caused by lime deposit in the calyces, (2) larger shadows of irregular density, some of which may assume the characteristics of renal stone, and (3) casts of a portion or even the entire caseated kidney. It is advisable, therefore, to have a complete roentgenographic examination of the urinary tract in every patient suspected of having renal tuberculosis.

*Shadow localization.*—It is of value to the surgeon to ascertain as accurately as possible prior to operation the exact location of the stone. Approximate localization of the stone shadow in the original roentgenogram is frequently possible, particularly if the outline of the kidney is distinct. By outlining the renal pelvis in a pyelogram and then comparing the position of the stone shadow with that of the pelvic outline, the stone can be localized more accurately than in the ordinary roentgenogram. The main problem in the localization of the stone is to determine whether it is situated in the true pelvis, in a calyx, or in the cortex.

Although the percentage of error in operations for lithiasis has been greatly reduced, several difficulties still remain to be overcome. The following are the complications which are most frequently encountered at the operating table:

1. Impossibility of an exact interpretation of the roentgenogram.
2. The difficulty of locating the stone in the kidney.
3. Inability to find the stone.
4. The possibility of overlooking one or more stones when multiple stones are present.
5. The possibility of having fragments of stones broken off or loosely connected with the original stone.

Nothing is more disconcerting than the inability to find a stone in the kidney when the various methods of clinical examination have definitely shown it to be there. The kidney usually becomes so congested when brought into the field of operation that searching for a small stone may be exceedingly difficult and often fruitless. Moreover, it may be difficult to determine from the roentgenogram the exact number of stones in a kidney. The shadow may appear to be single

when in reality it represents two stones which either overlap or are closely approximated. What appears to be a single branched stone may be made up of several distinct stones. Again, on the removal of a branched or irregular stone, fragments are easily broken off and it may be impossible to locate them. At the Mayo Clinic we have recently made fluoroscopic examinations of the kidney at the operating table, employing small portable x-ray machines which are used by the United States Army. By this method we believe that many of the difficulties accompanying renal lithotomy will be overcome.

*Renal functional tests.*—Although the surgical indications of the urinary tract are usually determined by the clinical, roentgenographic, and cystoscopic data, in many cases renal functional tests may be of considerable diagnostic value, and may largely influence surgical judgment. Tests of renal function are divided into two general types, excretory and retentive. The excretory test is the simpler of the two and is possibly the more valuable. Of the various excretory tests, the use of phenolsulphonephthalein has proved to be the most practical because of the accuracy of its elimination and ease of its administration. The original contentions of the authors, Rowntree and Geraghty, concerning the application of this test, have in the main proved to be correct. In the diagnosis of surgical conditions of the kidney it is used in estimating the renal function of both kidneys as in the combined test, and in the estimation of the secretion from the individual kidney as in the differential test.

*Combined phenolsulphonephthalein test.*—The phenolsulphonephthalein test as universally employed consists of the estimation of the dye secreted by both kidneys during two hours following its appearance in the urine after intramuscular injection of 1 c.c. of phenolsulphonephthalein. Its value in certain conditions is unquestionable, but attention should be called to the fact that errors may arise which, unless carefully watched, will largely negate its value. Such errors are of two types, technical and interpretative. If either of these errors occurs, the test is not only worthless, but may even be misleading.

*Technical errors.*—When the test is employed in a hospital where every step can be carefully guarded and the patient kept under observation during the time of secretion so that the specimen can be completely obtained, the possibility of technical error is not great. However, as generally employed in the dispensary, ambulatorium,

office, or at the bedside, the possibility of error is considerable. In our experience errors as follows have been found to occur most frequently:

1. Excessive or insufficient amount of phenolsulphonephthalein placed in the syringe for injection.

2. The loss of a portion of the phenolsulphonephthalein solution from the syringe or needle when it is injected.

3. Abbreviation or extension of the two-hour period of collection on the part of the patient.

4. Loss of part of the urine collected in transferring it into the receptacle from which the estimate is to be made.

5. Retention in the bladder of a portion of the urine secreted either because of a pathologic condition or misunderstanding on the part of the patient.

6. Error in laboratory technic, such as insufficient alkalization, inefficient interpretation of color values, and so forth.

7. Clerical errors.

Because of the many possible sources of error it is evident that a single phenolsulphonephthalein test with less than the normal amount of secretion must be considered worthless unless checked up by a second test.

*Errors of interpretation.*—Without placing an arbitrary figure which would govern in every case, as a general rule, a patient having a function of less than 30 per cent should be observed very carefully before advising operation. The possibility of retained urine at the time of the test from an overlooked prostate, diverticulum, sacculated ureter, or hydronephrosis must always be considered. However, even though the phenolsulphonephthalein secretion is lower than 30 per cent, it should not necessarily contra-indicate operation. It must be remembered that any renal functional test gives an index of renal activity at the time of examination but not what the kidneys are capable of when pathologic conditions have been corrected. This is particularly true in the presence of lithiasis; the reflex irritation from a stone may lower the function of one or both kidneys to an alarming degree. When, however, the cause has been removed it is not unusual to observe the renal function return to normal.

The assurance derived from a normal combined phenolsulphonephthalein test, when one kidney is definitely proved to be destroyed, is of great value. On the other hand, when the x-ray or clinical

examination indicates that one kidney is diseased, it cannot be inferred from a normal combined phenolsulphonephthalein test that the other kidney is present and normal. As an illustration; when a limited pathologic lesion such as a small stone, hydronephrosis, or even a limited area of tuberculosis is present in a single or solitary kidney, the combined phenolsulphonephthalein test may be quite normal. If it is inferred from this that another kidney is present the results at operation may be disastrous. The possibility of bilateral disease existing in the presence of a normal phenolsulphonephthalein secretion cannot be excluded since it has been repeatedly noted with bilateral tuberculosis, bilateral renal lithiasis, polycystic kidney, and so forth.

*Differential functional test.*—A differential functional test is the method of estimation of phenolsulphonephthalein secretion collected from the individual kidneys by means of the ureteral catheter during a period of from fifteen to thirty minutes following intravenous injection. Primarily the test was used to determine the state of efficiency of the supposedly well kidney. It is, however, of even greater value as an aid to diagnosis of renal lesion. As with the combined test, the possibilities of error in technic and interpretation must be considered. It is necessary that the dye be injected intravenously and not intramuscularly, otherwise the rate of secretion will be greatly retarded. If given intravenously the dye will appear in the urine within four or five minutes after injection, and an average of 15 and 30 per cent is secreted from each normal kidney in fifteen and thirty minutes respectively. The amount of dye, however, is not always constant and may be influenced by hypersecretion in a nervous person, which will cause a much larger amount of dye to be secreted, or by hyposecretion, which may be caused by reflex inhibition of secretion from catheter irritation. Another source of error may arise unless due allowance is made for return flow of the urine alongside the ureteral catheter into the bladder. It is necessary carefully to estimate the amount of dye which is found in the bladder at the end of the fifteen- or thirty-minute period.\* A recent suggestion of one of my associates (Peterson) has proved to be of practical value in this complication. He suggested a so-called "concentration test" which consists of estimating the dye in from 2 c.c. to 5 c.c. of the urine collected from each kidney and making a relative comparison. If the same amount of dye is found in both sides, even though a large amount of return flow

\* When more than 10 per cent of the total dye secreted is found in the return flow the value of the test is greatly diminished and may even be completely destroyed.



urine is in the bladder, we may infer that both kidneys are functioning equally.

The value of methylene blue and indigo-carmin as an aid to ascertaining renal function must, however, also be recognized. As a rough test, particularly when one or both kidneys cannot be catheterized or when it seems inadvisable to do so, it may be invaluable. Thomas has recently added to the value of the blue test by his method of making a quantitative estimate of the dye secreted. It is, however, not of such diagnostic value, nor is it so accurate in ascertaining the degree of renal function as the phenolsulphonephthalein test. It may occasionally be desirable to employ both tests simultaneously. Peterson has shown that the blue color need not interfere with the phenolsulphonephthalein estimate. He overcomes this difficulty by simply alkalizing the urine which removes the blue color and permits an accurate phenolsulphonephthalein estimate.

*Retention tests.*—Estimation of the degree of retention in the blood of metabolic end products such as uric acid, urea, and creatinin has of recent years been placed on a practical basis. This is largely the result of the work of American investigators such as Folin and Denis, Marshall, Myers and Fine, and others. The estimation of the urea nitrogen content of the blood has been most widely employed in surgical conditions of the urinary tract. It is generally recognized that an estimation of 40 mg. of urea nitrogen for each 100 c.c. of blood would indicate a guarded prognosis, and when it reaches more than 100 mg. the prognosis is very grave. More recently it has been found that creatinin when retained in the blood in amounts of more than 2.5 mg. is indicative of serious renal disease, and when more than 5 mg. is retained, the termination is usually fatal.

Retention tests are best employed in conjunction with the elimination tests. They are of considerable routine value in checking the results of the elimination tests and calling attention to possible technical errors in their estimation. Because of inability to obtain complete data of secretion, retention tests may offer the only method with which renal function can be estimated.

*Bacteriology.*—Probably the most important recent contribution to the bacteriology of the kidney is that made by Cabot and Crabtree, who have demonstrated that the clinical course of an infectious renal lesion is largely dependent on the identity of the bacteria. The colon group of bacilli tends to produce non-suppurative renal changes, while

the pathogenic bacteria, notably the cocci, tend to produce suppurative nephritis and abscesses. Lesions caused by the colon group are usually non-surgical and, in the early stages, are amenable to treatment, whereas a coccus infection of the kidney is distinctly a surgical condition. The coccus infections usually predominate in the cortex. The importance of making a bacterial investigation of the urine in cases of acute renal infections is self-evident.

The subject of renal infection, particularly as to the path of transmission of the original infection, has in recent years engaged the attention of numerous observers. Sweet, Eisendrath, and others have performed experiments which would go to prove the existence of an ascending or lymphatic route, while Cabot and Crabtree maintain that the infection is always hematogenous. It is probable that both methods of infection may exist although the latter is by far the more frequent. However, all observers are now quite convinced that renal infection is secondary to some other active focus of infection and that it is of primary importance to exclude the possibility of such a focus in the tonsils, teeth, prostate, seminal vesicles, and so forth.

Our knowledge concerning certain phases of renal physiology has recently been considerably augmented. The use of colloidal silver in the renal pelvis demonstrated to us the absorptive power of the renal parenchyma from the pelvis. This has been experimentally corroborated by Burns, and by Weld. It has been demonstrated that phenolsulphonephthalein injected into the renal pelvis is secreted from the other kidney within five minutes. This fact has been taken advantage of in the treatment of pyelonephritis by injecting large amounts of solutions of silver nitrate and other antiseptics into the renal pelvis. It may be inferred that not alone the pelvis will be affected, but the antiseptic solution will enter the renal tubules and come in contact with diseased areas in the parenchyma itself.

Theories as to the probable etiology of symptomless unilateral renal hematuria, or the so-called essential hematuria, have recently been modified. It was formerly thought that this condition was due to a true nephritis (Bright's Type 1 according to the classification of nephritis by W. J. Mayo). Recently, however, the condition has been regarded as frequently the result of an insidious chronic infection of the renal papillæ. Payne and MacNider, and Buerger have demonstrated that sections of the renal papillæ show evidence of infectious changes together with varicose condition of the venous capillaries.

It would seem that the circulatory changes in the papillæ are the direct result of the infection. This theory is further corroborated by the fact that permanent cessation of hematuria may be brought about by means of injecting strong solutions of silver nitrate into the renal pelvis. The diagnosis of this interesting condition is rendered fairly exact by demonstrating the outline of a normal pelvis in the roentgenogram and by demonstrating an equilateral normal phenolsulphone-phthalein output.

*Cystoscopic technic.*—The use of the cystoscope has, like the use of the roentgenograph, been widely extended in recent years. Many improvements have been made in the various instruments employed so that its value in diagnosis and treatment of diseases of the urinary tract has been greatly augmented. In the diagnosis of stones in the ureter the wax-tipped catheter which was suggested by Kelly many years ago, and which later fell into disuse, has recently enjoyed a renaissance. The method is as follows: Melted beeswax is placed on a ureteral catheter which is introduced up to or past a ureteral stone. If scratch marks result, they should be of considerable diagnostic value. Its practical application, however, particularly with the type of cystoscopes now in vogue, has not proved so satisfactory as it might seem. It often happens, particularly with small stones, that either no scratch appears or it is too indefinite for exact interpretation. Furthermore, scratches caused by the cystoscope may be difficult to identify. On the other hand, if properly employed the wax catheter should give data of considerable value.

Hunner has called our attention to the existence of wide strictures or infiltrations of the ureteral wall which have been overlooked in the past. He makes his diagnosis entirely from the obstruction or rather the hang encountered by a large wax bulb as it is passed through the strictured area. The frequency with which such a stricture occurs and the variety of symptoms it causes will make this condition one of primary importance if the findings of Hunner are corroborated by future investigation. The scarcity of pathologic and anatomic confirmation, however, in a measure negates the value of this contribution. Hunner furthermore claims that stones found in the ureter are usually formed in the dilated portion above a stricture rather than primarily in the kidney. Although the suggestion is of considerable interest it, nevertheless, lacks confirmation and seems improbable because of the following reasons: (1) The presence of a strictured area in the ureter

below a stone has not been corroborated by other surgeons. (2) Ureteral catheterization following operation fails to demonstrate strictures. (3) The small percentage of ureteral stones that recur even though no attempts are made to treat a stricture.

In conclusion I would say that recent progress in diagnosis of surgical conditions involving the kidney has indeed been considerable. The interest in the subject by both internist and surgeon is widespread since the close relationship of renal diagnosis to that of the surrounding organs is realized by both. Today there are but few medical groups that do not have access to such methods of diagnosis as I have described.

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## RENAL FLUOROSCOPY AT THE OPERATING TABLE\*

W. F. BRAASCH AND R. D. CARMAN

Surgical treatment of renal lithiasis is rendered unsatisfactory by complications as follows:

1. The difficulties of an exact interpretation of the roentgenogram.
2. The difficulty of locating the stone.
3. Inability to find the stone.
4. The possibility of overlooking one or more stones when multiple stones are present.
5. The possibility of having fragments of stones broken off or loosely connected with the original stone.

It is true that a large number of renal stones are easily diagnosed and removed. This is particularly true of stones with a diameter of two or more centimeters, situated in the pelvis. When the stone is small and flat, however, or when it is deep in the calyx projecting into the cortex, palpation of the stone may be impossible, even when the kidney is brought out of the incision. The possibilities of error in diagnosis have been greatly reduced through the aid of cystoscopy and pyelography. Nevertheless, it may be quite impossible (1) to differentiate extrarenal shadows which are obscured by the renal pelvis outlined in the pyelogram; (2) to identify small stones in the kidney that have not caused any pathologic changes in the outline of the renal pelvis; and (3) to recognize calcareous patches which are occasionally found in the kidney cortex and differentiate them from actual stone.

The preoperative localization of the shadow has been made fairly accurate (1) by interpretation of the size and shape of the shadow; (2) by the relation of the kidney to the shadow; and (3) by means of pyelography. Stones with a triangular or branched outline are almost always situated in the pelvis. If the outline of the kidney is definitely determined by the roentgenogram the position of the stone may frequently be approximately inferred. Although pyelography

\* Reprinted from Jour. Am. Med. Assn., 1919, lxxiii, 1751-1752.

will usually afford more accurate data in the localization of the stone, it may also be inexact. It may be impossible to determine whether the stone is free in the upper calyx, impacted in the end of the calyx, or projecting partially or wholly into the cortex.

Nothing is more disconcerting than the inability to find a stone in the kidney when the various methods of clinical examination have definitely shown it to be there. In the presence of a hydronephrosis, particularly when the dilatation is largely confined to the calyces, a stone of fair size may be secreted in the bottom of a calyx and defy discovery by the palpating finger. A stone lodged in the end of a calyx which is shut off from the pelvis by inflammatory or cicatricial change may escape palpation. When the stone is in the cortex the venous congestion of the kidney consequent to delivery may render its palpation exceedingly difficult. Needling, while occasionally of aid, is more often of doubtful value and since it causes considerable damage to the kidney tissue should be discouraged. Cortical incision, when extensive and multiple, is objectionable because of consequent destruction of renal tissue and the danger of subsequent hemorrhage.

It may be very difficult to determine, from the roentgenogram, the number of stones in a kidney. The shadow may appear to be single when in reality it represents two stones which either overlap or are closely approximated. What appears to be a single branched stone may be made up of several distinct stones. The shadow may be misleading when it has an evident projecting branch, which is seemingly explained by irregularity in the stone removed; a second small stone which actually caused the shadow may be easily overlooked. On the other hand, the shadow of an irregular stone may assume an outline and consistency suggestive of several stones. When only one stone is found at operation, the surgeon, after persistent search with more or less damage to the kidney, is still in doubt as to a remaining stone.

On the removal of branched stones, fragments are easily broken off, particularly when the ends are impacted in minor calyces. Examination of the stone removed may show this, but more often it cannot be determined definitely. Rough stones that are extracted with difficulty may have a soft fragment wrenched off. Occasionally soft stones have a putty-like mass of crystals adjacent to them which may later form the nucleus of another stone.

Because of the difficulties in interpreting the roentgenograms and

determining the number and location of stones, surgery for renal lithiasis is frequently an unsatisfactory procedure. Many so-called cases of recurrences of renal lithiasis are due to the fact that the stone or stones have not been completely removed at the time of operation. Whether or not stones or their fragments have been overlooked may often be determined by a roentgenogram made following convalescence from operation. This may give the desired information; but if a shadow persists the patient's condition will not be improved, and the surgeon is then faced with the awkward necessity of being obliged to advise either an immediate or postponed operation. An immediate operation is rendered difficult by the patient's condition, by changed conditions of the perirenal tissues, the possibility of renal hemorrhage, and so forth. If the operation is postponed the patient may neglect the condition until the kidney becomes seriously damaged.

Realizing the difficulties involved it is apparent that a more accurate method of examination of the kidney at the time of operation is desirable. Unfortunately the usual roentgenographic examination at the operating table is an awkward procedure and requires too much time. It would seem that if fluoroscopic examination when the kidney is brought out of the wound could be made practical the various difficulties surrounding lithotomy would be readily overcome. Taking advantage of the recent improvement made in fluoroscopic apparatus and the simplification of roentgenographic machines, we have employed the apparatus described herewith.

*Apparatus.*—The apparatus used for making fluoroscopic observations of the kidney at the operating table is essentially the same as that used in the base and field hospitals of the army, but with certain minor changes which make it adaptable to civilian practice.

Such instruments (machines) consist of a transformer and auto-transformer enclosed in a metal cabinet mounted on large casters for portability. To the cabinet is attached a tube stand with a horizontal arm having universal joints for supporting the tube. The tube is of the Coolidge radiator self-rectifying type mounted in a lead glass shield.

The unit is small and compact, requiring less than two and one-half square feet of floor space. It is of light weight, portable, and has no moving parts which might cause noise and vibration. The current is turned on and off either by a hand or floor switch. These portable



units may be operated from the ordinary lamp socket without special wiring.

*Technic.*—As an essential preliminary, the x-ray operator should wear goggles of smoked glass for about fifteen minutes before the observation is to be made in order that he may have the necessary dark-accommodation and retinal perception. The x-ray unit should be placed as close to the operating table as possible, and the rays focused through a small diaphragm so that they will pass through the delivered kidney onto the fluoroscopic screen. When the fluoroscopist is ready to make the x-ray examination, the hooded screen held in the left hand is placed over the eyes, and the goggles are removed. The current is turned on by means of a foot switch. In the right hand is held a sterilized metal-tipped rod 18 inches long which the fluoroscopist accurately points to the stone shadow in the kidney. The exposure is short, requiring little more than a flash. The various details can be easily arranged so that there is no interference with surgical asepsis.

## SURGICAL RENAL TUBERCULOSIS: THE PROGNOSIS\*

W. F. BRAASCH

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Several factors affecting the prognosis in cases of surgical renal tuberculosis have not as yet been definitely determined. Probably the most important of these are: Age, sex, coincident tuberculosis in other tissues, duration of symptoms, degree of involvement of the bladder and kidney, and bilateral renal disease.

According to the surgical records of the Mayo Clinic 532 persons were operated on for renal tuberculosis from Jan. 1, 1894, to Jan. 1, 1918. During this period about 85,000 patients were operated on; thus the incidence of surgical renal tuberculosis may be estimated as 0.6 per cent. A previous review<sup>1</sup> has been made of the postoperative records of a portion of these cases, but the present data have been derived from more complete records and a larger number of cases.

The total number of patients (532) was employed in the estimation of many of the general statistics. Among this number were 16 patients who were known to have bilateral renal tuberculosis and were therefore not considered in the survey of postoperative results. Statistics bearing on postoperative results were based on the postoperative records of patients heard from either by correspondence or by personal examination. This number included 435 patients (84.3 per cent) of those operated on. It will be noted that only the postoperative records of patients operated on prior to Jan. 1, 1918, were studied. In considering the influence of the different complications it was found that more detailed data were available in 346 cases in which operations were performed from Jan. 1, 1912, to Jan. 1, 1918, inclusive.

The greatest incidence of surgical renal tuberculosis (69 per cent of the total) occurred between the ages of 20 and 40. The largest number of cases (37 per cent) was in the third decade. The condition is rarely found in the first and seventh decades. When tuberculous

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infection of the kidney does occur in children, it is usually in conjunction with tuberculosis disseminated in other tissues so that operation is inadvisable. Nephrectomy in children should not be done with the first onset of symptoms; it is advisable only when it is evident that the active tuberculous infection is localized in the kidney.

TABLE 1.—AGE

Patients operated on.....	532	
		Per cent
2 patients 0 to 10 years.....		0.4
37 patients 11 to 20 years.....		6.9
197 patients 21 to 30 years.....		37.0
168 patients 31 to 40 years.....		32.0
89 patients 41 to 50 years.....		16.7
36 patients 51 to 60 years.....		6.7
3 patients 61 to 70 years.....		0.6
Patients with postoperative data.....	435	
	Reported dead	Per cent
32 patients 11 to 20 years.....	9	28.1
161 patients 21 to 30 years.....	41	26.2
137 patients 31 to 40 years.....	26	18.9
75 patients 41 to 50 years.....	20	26.6
27 patients 51 to 60 years.....	7	25.9
3 patients 61 to 70 years.....	1	33.3

The influence of age on the ultimate prognosis is of comparatively little significance and the general mortality average remains fairly constant in the various decades. The late mortality during the third decade is somewhat lower than that during the other decades, but the difference is not great enough to warrant any definite prognostic distinction. In the first and last decades too few cases are involved to give the mortality percentage any accurate value.

TABLE 2.—SEX

Patients.....	532	Per cent
Males.....	338	63.5
Females.....	194	36.5
Patients with postoperative data.....	435	
Deaths.....	105	
Males.....	75	27.5
Females.....	30	18.4

The greater number of male patients is in keeping with the preponderance of male patients in cases of other chronic infections of the

kidney. The relative mortality is somewhat higher in the male. The relative duration of preoperative symptoms is practically the same in both sexes.

TABLE 3.—COINCIDENT LESIONS

		Per cent
Patients with renal tuberculosis operated on from 1912-1918.....	346	
Patients with coincident lesions.....	244	71.0
Patients with complete postoperative data.....	201	
Patients who died.....	33	16.4
Patients with one lesion.....	89	
Patients with one lesion who died.....	14	15.7
Patients with two lesions.....	56	
Patients with two lesions who died.....	9	17.8
Patients with three lesions.....	39	
Patients with three lesions who died.....	5	12.8
Patients with more than three lesions.....	17	
Patients with more than three lesions who died..	5	29.4

Evidence of tuberculosis in other parts of the body, either healed or active, was found in 244 of the 346 patients (71 per cent) operated on since 1912. In the examination of a patient with suspected renal tuberculosis a thorough search for such complications is necessary. In fact, it is questionable whether renal tuberculosis ever occurs without coincident tuberculosis in some other tissue, and which may not be apparent on casual examination. That such complications exert but little influence on the ultimate prognosis is evidenced by the fact that the mortality percentage in our cases was even lower when coincident tuberculosis was noted than that of the general average. The occurrence of coincident tuberculosis, particularly when healed or dormant, does not necessarily render the prognosis less favorable; in fact, it may be regarded as an evidence of good resistance power on the part of the patient. In reviewing the postoperative results of the patients with complications it is of interest to note that when multiple lesions occurred the percentage of recovery was relatively as great as when only one lesion was noted. The only exception occurred where multiple active complications existed as a part of a generalized tuberculosis. The individual influence of the various coincident tuberculous lesions will be considered separately.

Pulmonary tuberculosis is one of the most common complications occurring with renal tuberculosis. Fortunately it is usually found in a chronic or healed form. Renal tuberculosis is not a common complication of active pulmonary tuberculosis. It occurred as a

coincident infection in less than 5 per cent of our patients. As a part of a general or a miliary tuberculosis the coincident infection probably occurs more frequently. Pulmonary tuberculosis as a secondary complication of renal tuberculosis is of relatively infrequent occurrence although it is a factor in the late mortality after nephrectomy.

TABLE 4.—COINCIDENT PULMONARY TUBERCULOSIS

		Per cent
Patients operated on for renal tuberculosis, 1912-1918.....	346	
Patients having complete postoperative information.....	298	
Patients who died.....	44	14.7
Patients having complete x-ray and clinical examination of chest.....	300	
Patients having definite evidence of pulmonary involvement.....	81	27.0
Patients having definite active tuberculosis.....	16	5.3
Patients having definite active tuberculosis and complete postoperative information.....	13	
Patients who died (none in hospital).....	6	46.3
Patients having doubtful active tuberculosis.....	17	
Patients having doubtful active tuberculosis and complete postoperative information.....	16	
Patients who died.....	3	18.7
Patients having definite healed tuberculosis.....	26	
Patients having definite healed tuberculosis and complete postoperative information.....	21	
Patients who died.....	2	9.5
Patients having indefinite clinical or indefinite evidence of previous pulmonary involvement.....	22	
Patients having complete postoperative information.....	19	
Patients who died.....	1	5.2

Complete x-ray and clinical examinations were made of the chest in 300 patients. Evidence of pulmonary tuberculosis was found in 84 (28 per cent). The cases were divided into four groups: (1) Definite active tuberculosis; (2) doubtful active tuberculosis; (3) definite healed tuberculosis; and (4) doubtful clinical or x-ray evidence of previous involvement. A number of patients in whom the physical and x-ray data were indefinite were not included.

In Group 1 were 16 patients (4.6 per cent) of the total number operated on. Fourteen were males and 2 were females. The mortality of this group as might be expected was very high; 6 (37.5 per cent) of the patients died. However, since almost two-thirds of the patients recovered it is evident that active pulmonary tuberculosis does not necessarily exclude operation in cases of renal tuberculosis, but, on the contrary, offers a fair chance for recovery. In the majority

of these cases the active pulmonary lesion was confined to comparatively limited areas, diffuse miliary involvement being regarded as excluding operation. In several cases, although the lesions were quite extensive and even bilateral, the general condition of the patients warranted operation. In several cases of well-advanced pulmonary tuberculosis the advisability of operation was doubtful, but it was rightfully argued that an operation offered the only chance of recovery. The most important factor in determining the advisability of operation was the patient's general condition. None of the patients died in the hospital, or immediately following operation, showing that the anesthetic (ether in every case) even in the presence of active pulmonary tuberculosis had no immediate harmful effect.

Group 2 probably includes a small number of patients with limited active lesions. The mortality was approximately average. In Groups 3 and 4 the mortality was unusually low. From this it may be argued that patients with healed pulmonary tuberculosis have developed high resisting powers against the tuberculous infection, and that complicating renal tuberculosis is an evidence that the resistance of patients is only temporarily lowered at the time of the renal infection.

TABLE 5.—GENITALIA

		Per cent
Male patients operated on (1912-1918).....	234	
Lesions in genitalia.....	171	73.0
Complete postoperative data.....	141	
Patients reported dead .....	26	18.4
Epididymectomy prior to operation.....	26	
Epididymectomy after operation.....	24	
Patients who died following epididymectomy after operation.....	3	12.5

Coincident tuberculosis in the genitalia rarely occurs in the female; it was noted as definite in 171 (73 per cent) of the group of 234 male patients. Twenty-six of these patients (18.4 per cent) died, 13 during the first year. The late mortality is therefore not greatly influenced by this complication. The high percentage of recoveries among the patients in this group who had clinical evidence of tuberculosis in the prostate and seminal vesicles should contra-indicate surgical treatment of these organs. It is evident that spontaneous healing must occur in the majority of instances. On subsequent examinations the prostate and vesicles are usually diminished in size, and either hard and fibrous or apparently practically normal. Acute suppuration in

the prostate and seminal vesicles is unusual. Surgical treatment of the tuberculous prostate is indicated only in certain cases of protracted vesical irritation or in the presence of suppuration.

Tuberculosis in the epididymis and testicle should be treated surgically because of the frequency of suppuration and because the process does not usually become dormant and disappear. Furthermore, a tuberculous epididymis must always be regarded as a possible focus of general infection. Epididymectomy was done on 50 patients in the series: 26 prior to nephrectomy and 24 following nephrectomy. Three (12.5 per cent) of the last group are reported dead.

TABLE 6.—BONES AND JOINTS

		Per cent
Patients with lesions.....	21	6.0
Patients with complete postoperative data.....	19	
Patients with lesions described as active.....	10	57.8
Patients reported dead.....	1	5.2
Patients with spondylitis.....	17	5.7
Patients with active spondylitis.....	3	
Patients reported dead (1 active spondylitis).....	2	11.7

Tuberculosis, either healed or active, involving the bones and joints, is not unusual with renal tuberculosis. A review of our records shows 21 (6 per cent) such cases. Of this number 10 were described as active. Four (13.3 per cent) of the patients are reported dead. Coincident lesions in the bones, even though active, have little or no bearing on the prognosis provided it is not a part of general acute tuberculosis.

To the group of complications involving the bone should be added the cases of spondylitis. Fourteen patients were suffering with chronic and three with active spondylitis. Two of the former and one of the latter are reported dead, evidence that chronic spondylitis does not greatly affect the ultimate result. Active spondylitis, particularly in the presence of other tuberculous lesions, will necessarily make the prognosis much more serious, but it does not contra-indicate operation. One of the patients with an active process operated on six years ago is living, in a fair degree of health. In a number of such patients observed the condition was regarded as inoperable either because of their general health or the presence of other active complications.

*Adenitis.*—In but 19 (6.4 per cent) patients was there any well-marked evidence of tuberculous adenitis. In the majority of these only a few glands were involved, and in none sufficiently to require sur-

gical intervention. Two of the 19 patients (10 per cent) are reported dead, indicating that this complication has no bearing on the prognosis other than to show the high resistance on the part of the patient.

TABLE 7.—HEMOGLOBIN

Patients having less than 80 per cent.....	73
Patients reported dead.....	7 (9 per cent)
Average duration of bladder symptoms (2 cases without)...	2 years, 9 months
Patients with 50 per cent or below (one died).....	8

Anemia secondary to renal tuberculosis is frequently noted. Its incidence in our series was 25 per cent. As a rule the degree of anemia is not marked. The reduction in hemoglobin is seldom caused by the loss of blood from hematuria. It is not in proportion to the duration of symptoms of the bladder since a number of patients with low hemoglobin had symptoms of only a few months' duration. The average duration was two years and seven months, which is about the average of all cases. The greatest reduction of hemoglobin is noted with extensive renal suppuration when absorption of toxins was evidently the cause. The degree of hemoglobin gives no index to prognosis; 8 patients had 50 per cent hemoglobin, or below, of whom 1 died. Seven patients in the series (9 per cent) are reported dead.

TABLE 8.—BLADDER INVOLVEMENT

	Patients	Dead	Per cent
Degree 1.....	55	8	14.5
Degree 2.....	92	9	9.7
Degree 3.....	71	16	22.5
Degree 4.....	43	7	16.2

The pathologic condition in the bladder as noted on cystoscopic examination in this series is estimated on a scale of 1 to 4; 1 slight involvement; 2 moderate; 3 marked, and 4 extreme. It was found that the patients were about equally divided between moderate (1 and 2) and marked (3 and 4), the largest single group being 3. The average duration of preoperative symptoms when the degree of inflammation was scaled 3 and 4 was two and one-half years, and when it was scaled 1 and 2 it was only one and one-half years. When the preoperative degree of bladder inflammation was slight or moderate (1 and 2) it was found that immediate postoperative improvement in bladder symptoms occurred in 20 per cent, whereas with bladder inflammation graded 3 and 4 immediate improvement was noted in only 10 per cent. The late mortality in cases of moderate bladder involvement (1 and 2)



was practically 11 per cent, whereas with advanced involvement (3 and 4) it was 20 per cent or twice as great. Although the renal disease usually has existed longer in cases of marked bladder involvement, the difference in involvement is evidently more dependent on the virulence of the infection than on the duration of symptoms.

TABLE 9.—DEGREE OF PATHOLOGY

		Per cent
Patients with complete postoperative data (1912-1918).	298	
Patients dead.....	44	14.7
Patients with limited lesion.....	37	
Patients dead.....	2	4.5
Patients with advanced lesion.....	159	
Patients dead.....	25	15.7
Patients with large pyonephrosis.....	58	
Patients dead.....	12	20.6
Patients with occluded tuberculosis.....	44	
Patients dead.....	5	11.3

The conditions of the kidneys removed were divided into four groups: (1) Slight lesions; (2) advanced lesions; (3) complete destruction, described as advanced pyonephrosis; and (4) occluded (caseated) tuberculosis. The lesions in the first group were slight, consisting of limited single areas, or multiple early lesions. The mortality in this group (4.5 per cent) was the lowest and seems to refute the necessity of the patient's development of immunity before the kidney is removed. In by far the largest number of patients the pathologic condition of the kidneys was described as advanced (Group 2). Multiple areas involving from one to two-thirds of the kidney substance were usually found. In Group 3 cases the process has generally existed for so long a time that extensive suppuration has occurred. The mortality is greatest and is probably explained by absorption of toxins from the extensive abscesses with consequent damage to the other organs. Nevertheless, the most gratifying results are frequently obtained among patients in this group, who before their operation are often in extremely poor general condition and afterward become quite normal. Group 4 is in reality a group by itself. It is composed of patients in whom nature has occluded the ureter, performing a so-called autonephrectomy, and the tuberculous process is supposed to have run its course. In only a few such cases was there any evidence of active tuberculosis in the kidneys; in the majority, the original kidney tissue had undergone caseation. The low mortality is evidenced by the patient's high resisting powers.

TABLE 10.—DURATION OF PREOPERATIVE SYMPTOMS

	Cases	Not changed or slightly improved	Per cent	Markedly improved or practically well	Per cent	Dead	Per cent
1 to 3 months.....	30	4	13.3	18	60.0	8	26.6
4 to 12 months.....	162	33	20.3	87	53.7	42	25.9
1 to 5 years.....	155	40	25.8	71	45.8	44	28.3
5 years.....	57	23	40.3	27	47.3	7	12.2
Indefinite.....	31	4	12.9	23	74.1	4	12.9
Total.....	435	104	23.9	226	51.7	105	24.1

The influence of the duration of preoperative symptoms on the prognosis might be considered from three phases: (1) Its relation to the severity of the bladder infection; (2) the time elapsing before postoperative improvement; and (3) the postoperative mortality.

Although the severity of the bladder infection is largely dependent on the length of the preoperative symptoms there are other influential factors. It is not uncommon to observe marked inflammation and ulceration with symptoms of only a few weeks' duration. On the other hand, a fairly normal bladder is occasionally found when the disease has evidently existed many months. Further, with occluded renal tuberculosis when the initial symptoms had occurred and ceased several years before, the cause of the bladder infection having been removed by autonephrectomy, the bladder usually became fairly normal.

In the majority of cases the duration of vesical symptoms persisting after operation diminished in direct proportion to the length of preoperative symptoms. Of the patients with preoperative symptoms of less than three or four months' duration improvement was noted immediately in 48 per cent. When the symptoms existed a year or more prior to operation immediate improvement was noted in only 15 per cent.

A review of the mortality records shows that there is surprisingly little difference in the mortality with regard to the length of preoperative symptoms of less than five years. It has been claimed that the mortality of patients with short duration of symptoms is considerably higher than that of patients with long duration, and that a relative degree of immunity is established among the latter. This, however, was not borne out in our cases, since the group of patients with symptoms of less than three months had practically the same mortality as

the group in which the symptoms were of much longer duration. It is of interest that the mortality in the group of patients having symptoms more than five years is considerably less than the average. This is explained by the fact that many of these patients had either an occluded renal tuberculosis or a high degree of immunity. This group also included 5 patients who had no evidence of disease other than albuminuria and slight pyuria, and in whom the discovery of renal tuberculosis was largely accidental.

TABLE 11.—BILATERAL RENAL TUBERCULOSIS

Patients with definite bilateral involvement.....	16
Patients reported dead (none alive longer than one and one-half years.....)	13
Patients living (less than two years after operation).....	3

It has been claimed that in cases of bilateral renal tuberculosis if the more diseased kidney is removed the patient will often improve, and in certain instances recover. It has also been claimed that infection in the remaining kidney may be reduced or overcome by compensatory hypertrophy; this has not, however, been substantiated by the end results in our series of bilateral cases. Thirteen of the 16 patients with proved bilateral renal tuberculosis are reported dead; 3 are living. None of the 13 patients lived more than one and one-half years after operation, and all but 3 died in less than six months. The 3 patients living were operated on two years before their last report. One of these became steadily worse and recently had complicating perineal fistulas. The general health of the other two has temporarily improved. Both patients had a large active tuberculous pyonephrosis on one side, which was removed, and a fair degree of function in the other kidney. Such patients improve because the toxemia of acute infection is removed, and not because of improvement in the other kidney. When an occluded caseated kidney was removed, little or no benefit followed. Unless one kidney is largely destroyed and the other is in fair condition, operation should not be considered; and then only when infection, pain, or possibly hemorrhage renders it imperative. Many cases of bilateral renal tuberculosis in which cure by operation was reported in the literature were probably not bilateral. Doubtless pus or tuberculosis bacilli picked up by the ureteral catheter

from an infected lower ureter, while the kidney itself was normal, could best explain such results.

TABLE 12.—MORTALITY

		Per cent
Operations for unilateral renal tuberculosis.....	516	
Operative mortality.....	7	1.3
Patients with complete postoperative data.....	435	
Deaths.....	105	24.1
One year or less after operation.....	58	55.2
Two years after operation.....	8	
Three years after operation.....	6	
Four years after operation.....	2	
Five years after operation.....	7	
Six years after operation.....	5	
Seven years after operation.....	3	
Eight years after operation.....	1	
Nine years after operation.....	1	
Ten years and more after operation.....	1	
Date of deaths not given.....	13	

The operative mortality (1.3 per cent) is a comparatively negligible factor. The total mortality (excluding bilateral renal tuberculosis) is 24 per cent, which includes every death from any cause following operation, some occurring as long as ten or more years afterward.

Fifty-eight patients (55 per cent) died within one year after operation. The relatively high mortality during the first year after operation has been previously noted by several observers. It would seem logical to regard the early death as an evidence of the virulence of the infection rather than as a result of the operation. It may be inferred that the probability of death from tuberculosis decreases inversely with the length of time after operation. Owing to the inability to get accurate data as to the cause of postoperative death, no attempt was made to investigate this factor.

Many patients died from diseases other than tuberculosis and from accidents, so that the late mortality from tuberculosis is really much less than our figures indicate. Furthermore, a considerable proportion of the total number of deaths reported occurred more than five years after operation. It would be conservative and more accurate, therefore, to regard the actual late mortality as not more than 20 per cent.

One hundred four (23 per cent) of the living patients stated that they had not entirely recovered from their bladder symptoms. From many of these answers to inquiries were received in less than two

years after operation, and it is safe to assume that at least 5 per cent would eventually report recovery from their symptoms. Moreover, 64 patients reported a gain in weight and general condition, so that except for the bladder symptoms they were in a fairly good state of health.

It may be assumed, therefore, that approximately 80 per cent of the patients will recover following operation for renal tuberculosis and that a complete cure, including cessation of urinary symptoms, may be expected in fully 60 per cent.

#### CONCLUSIONS

1. Renal tuberculosis occurs most frequently between the ages of 20 and 40 (70 per cent).
2. It occurs in the male almost twice as often as in the female.
3. The postoperative mortality in the male patient is somewhat higher than in the female.
4. The condition is usually not surgical in children; it occurs more often as a part of a general tuberculosis.
5. Evidence of tuberculosis in other tissues of the body may be found in fully 71 per cent of the patients, if not in all.
6. The postoperative mortality among patients with coincident lesions is not higher than that of the general average.
7. Multiple lesions, unless they are a part of an acute general infection, do not necessarily render the prognosis more unfavorable.
8. Evidence of healed pulmonary tuberculosis is present in fully one-third of the patients.
9. The percentage of recovery among patients with healed pulmonary tuberculosis is above the average and may be considered indicative of increased powers of resistance.
10. Coincident active pulmonary tuberculosis was found in approximately 5 per cent of the patients, of whom more than 60 per cent recovered following nephrectomy.
11. Involvement of genitalia is present in at least 73 per cent of male patients and does not seem to affect the ultimate recovery.
12. Frequency of spontaneous healing of lesions in the prostate and seminal vesicles contra-indicates their removal by subsequent operation.
13. Evidence of tuberculosis involving the bones and joints was

noted in 6 per cent of the cases; one-half of the lesions were active. The late mortality was 5 per cent, from which it may be inferred that the presence of such complications may be an index of increased resistance.

14. Spondylitis, usually healed, was present in 5.7 per cent, with a mortality of 12 per cent.

15. Chronic spondylitis does not influence the prognosis. Active spondylitis, although it does not contra-indicate nephrectomy, will not offer a favorable prognosis.

16. Tuberculous adenitis was present in 19 patients (6.4 per cent) and the low mortality (10 per cent) is suggestive of a heightened resistance.

17. Reduction in hemoglobin does not necessarily affect the prognosis.

18. The mortality among patients with marked bladder involvement is twice as great as with slight involvement. The degree of involvement is dependent not so much on the duration of symptoms as on the virulence of the infection.

19. The mortality percentage is markedly influenced by the degree of pathologic involvement of the kidney, increasing in proportion to the extent of the lesion. Early lesions have the lowest mortality and pyonephrosis the highest.

20. Occluded renal tuberculosis is indicative of relative immunity and a low mortality.

21. The duration of preoperative symptoms does not materially affect the late mortality.

22. Recovery from bladder symptoms is more apt to occur, and earlier, when the preoperative symptoms are short than when they are long.

23. Recovery or permanent improvement of the remaining kidney will not follow after one kidney has been removed in cases of bilateral renal tuberculosis.

24. Operation in cases of bilateral renal tuberculosis is advisable only when there are acute unilateral complications, and then with no hope of eventual recovery.

25. Late mortality is much the highest during the first year; it decreases with the length of time elapsing after operation.

26. The operative mortality is a negligible factor; the late mortality (five years or less after operation) is approximately 20 per cent;

failure to effect complete cure is approximately 20 per cent; this leaves a prognosis of recovery in 80 per cent and of a complete cure to be expected in fully 60 per cent of patients.

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## PAPILLARY TUMORS OF THE PELVIS OF THE KIDNEY\*

E. S. JUDD

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Papillary tumors are seldom found in the pelvis of the kidney or in the ureters, although they are common among lesions of the bladder. Israel reported only 2 cases of papilloma of the pelvis of the kidney among 68 cases of renal tumors. Watson and Cunningham found only one such lesion diagnosed among 94 cases of renal and perirenal tumors collected at the Boston hospitals during a period of ten years. Albarran found 42 cases of pelvic renal tumor reported in the literature up to 1900. Eighteen of these were papillomas; 6 had invaded the ureter; 4 of the 6 extended also to the bladder. Suter reports having found a solitary papilloma in the lower end of one ureter which had caused very profuse hemorrhages. The kidney and bladder were explored, but bleeding from the ureter continued after the kidney was removed; the lesion was not discovered until the ureter was removed. Battle describes a case of calculus in the kidney and papilloma in the renal pelvis. After the extraction of the stone and conservative removal of the tumor, the growth recurred, and a nephrectomy was performed. Lower reports a case of malignant papilloma of the pelvis of the kidney with transplantation into the ureter and bladder, which is apparently very similar to the case I shall report.

The genesis of papilloma of the kidney is not clear. Stones occur in the pelvis of the kidney in about 15 per cent of the cases, and these have been suggested as a possible etiologic factor. The papillary structure is regarded as proliferating epithelium of the renal pelvis, and the exact nature of the tumor seems to be based on the appearance of the epithelial cells within the connective tissue beneath the tumor. The presence of these cells as a distinguishing feature has been questioned by those who contend that epithelial cells are normally present in the form of glands in this tissue. Morogna recently reported

\* Presented before the Minnesota Academy of Medicine, February, 1919.  
Reprinted from *Journal-Lancet*, 1919, xxxix, 247-253.



2 cases of renal pelvic tumor, and gave a detailed study of the histology with a very complete review of the possible etiologic factors



FIG. 100 (212016).—a. Kidney with pelvis and upper segment of ureter. The incision has been made in the pelvis and the papillomas forced outward. b. Lower end of ureter with multiple papillomas, which probably extend downward into the bladder.

suggested by other authors and by himself. He believes that it is possible, though not demonstrable, since thus far it has not been

proved that the tumors develop by metaplastic evolution; that the formation of papillomas of the renal pelvis may be explained by the occurrence of aberrant ectodermal inclusions during the period of development, excited to proliferation by an inflammatory process.

Papillary tumors of the pelvis of the kidney are unlike the papillary adenomas that occur in the parenchyma of the kidney, as the pelvic



FIG. 101 (212016).—The open kidney and the exposed papillomas rising from the mucous membrane of the pelvis.

tumor does not invade the kidney substance at any point; its growth and extension is in the pelvis itself, and it has a tendency to pass down the ureter. The papillary adenomas originate from the epithelial cells of the parenchyma, while the squamous-cell papillomas start from the epithelium of the pelvis of the kidney. The latter may be compared with the intracanalicular papillomas that occur in the ducts of the mammary gland, while the former may be compared

with the cystadenomas that occur in the breast. Papillary tumors of the pelvis of the kidney are usually, if not always, multiple. These neoplasms may be divided into three classes: (1) the simple papillomas which show throughout their entire development and evolution the characteristics of all such tumors; (2) the epithelial papillomas which almost immediately show the characteristics of malignancy; and (3) those tumors which apparently change from a supposedly benign to a malignant growth. The same question arises with regard to the features distinguishing these benign and malignant papillomas as arises with regard to papillomas of the bladder. For practical pur-



FIG. 102 (212016).—Photograph of papillary squamous-cell tumor of the pelvis of the kidney (closed).

poses it would seem best to credit malignant tendencies to all of these papillomas, and treat them in a more or less radical manner.

The particular case of squamous-cell papillary tumor of the renal pelvis which I shall report occurred in a priest aged 55. In nearly all of the reported cases the condition has occurred in men past 45. This patient consulted us in October, 1917. His chief complaint was hematuria. He had considered himself well until January, 1917, at which time he first noticed blood in the urine. The amount of blood was not great at any time, although it had persisted continuously since he first noticed it. He had no pain nor irritability of the bladder,

and there had been no difficulty in voiding, but there was some trouble in retaining the urine. He mentioned having a slight frequency of urination, which caused him to get up once or twice at night. Two or three cystoscopic examinations had been made elsewhere, and the patient had been told that the left ureter was obstructed, that the blood in the urine was coming from the left side, and that the left kidney was functionally impaired.

In reviewing the records of this case of papillary tumor of the pelvis of the kidney, I also briefly reviewed our records of other tumors of the kidney. While Case 1 was found to be the only instance of



FIG. 103 (212016).—Kidney shown in Figure 102, with pelvis open.

definite papilloma of the kidney and ureter in the entire series of 207 cases of tumor of the kidney, in one other case (Case 2) the tumor had so completely destroyed the kidney that it was difficult to determine just where the lesion had originated. Dr. Broders, who made a histologic study of the cases in this series, believes that the second case should also be classified as a squamous-cell papillary tumor of the pelvis of the kidney. The statistics in the literature and those in our own records emphasize the fact that papillary tumors of the pelvis of the kidney are rare forms of renal tumors. They should, nevertheless, be borne in mind in the examination of such

cases, particularly when a papilloma presents itself at the ureteral meatus.\*

**CASE 1 (212016).**—The patient was large and obese. A specimen of urine showed considerable blood. An estimate of the kidney function showed a 40 per cent. phenolsulphonephthalein output in two hours, and 22 mg. of blood urea to 100 c.c. All the urine came from the right side. A diagnosis was made of surgical left kidney containing a tumor, or of a polycystic condition.

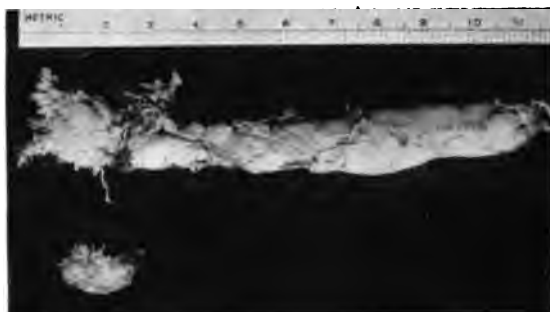


FIG. 104 (212016).—Photograph of squamous-cell papillary tumor of the ureter (closed).

**Operation, Nov. 7, 1917:** A left anterior abdominal incision was made for the purpose of general exploration, but this revealed nothing of a pathologic nature in the abdomen. The right kidney seemed normal. A tumor could be palpated in the pelvis of the left kidney. The abdominal incision was extended laterally, and the left kidney and 4 inches of the left ureter removed. The kidney proved to be about normal in size, except that the pelvis and the upper end of the ureter were much dilated. The pelvis of the kidney was about 4 inches in length and more than 2 inches in depth and breadth. A soft tumor could readily be palpated in the dilated pelvis and ureter. The

\* Since this paper was written, Dr. C. H. Mayo has operated in a similar case of squamous-cell papillary tumor of the kidney. A papilloma was found presenting at the left ureteral meatus. The growth was rather small, and responded to fulguration treatment. The patient was kept under observation for about three weeks. His bladder appeared to be entirely healed, when he had a severe attack of bleeding; the blood came from the ureter in the area in which the papilloma had been fulgurated. A functional test of the kidneys showed this particular kidney to be almost without function; the work was being done by the other kidney. The left kidney and ureter were removed, revealing a definite papillary tumor of the pelvis of the kidney with involvement of the ureter. This case is of particular interest because of the fact that the patient was only thirty-four years of age, and came to the Clinic with a diagnosis of tumor of the bladder, a condition naturally accountable for all his symptoms. The tumor of the kidney was not discovered until after the condition of the bladder had entirely cleared up.

dilatation in the ureter extended down more than 2 inches, and then the ureter abruptly became normal in size and appearance. A nephrectomy was done, and the diseased portion of the ureter, with more than 2 inches of normal ureter, was removed; the distal end was ligated and allowed to drop back into the wound. On opening the kidney pelvis and the ureter, a large papilloma was found. The capsule, cortex, and parenchyma of the kidney appeared to be in good condition. Papillary projections of the tumor extended into the dilated calices; they originated from the mucous membrane of the pelvis of the kidney and the upper ureter. The tumor was identical



FIG. 105 (212016).—Photomicrograph of squamous-cell papillary tumor of the pelvis of the kidney.

in appearance with the papillomas of the bladder that are so common. (Figs. 100 to 106.)

**Histologic examination:** The growth was diagnosed as a malignant papilloma. The neoplasm was made up of a proliferation of squamous epithelial cells on fine connective-tissue pedicles. In places the epithelium seemed to break through into the connective tissue, and show definite malignant tendencies. A large part of the mucous membrane of the pelvis of the kidney was normal. The tumors were on small pedicles and made a mass of considerable size.

The patient made a satisfactory recovery after the operation, and was dismissed in a short time with his wound entirely healed. He

returned to his duties, and remained well for about nine months. In August, 1918, he again had trouble and passed a rather large amount of blood in the urine during one urination only. He had no further trouble for three months, when he again began to pass blood and blood clots. This was repeated several times prior to his second examination; the urine always cleared up again, and the patient was well. When he presented himself a second time, the urinalysis was negative with the exception of a few blood cells. Cystoscopic examination showed a cauliflower papillary growth at the site of the left meatus about three-fourths of an inch in diameter. The growth extended almost to the meatus of the urethra; an entirely separate growth was noticed in the trigone.



FIG. 106 (212016).—Squamous-cell papillary tumor shown in Figure 104. ureter open.

Jan. 3, 1919, a second operation was performed. A large extra-peritoneal opening was made in the dome of the bladder, and the papillomas were seen bulging from the left ureteral meatus. There was also a separate papilloma, apparently a graft, on the base of the bladder close to the urethra. The tissues in the left prevesical space were separated, and the left ureter, which was several times the normal size and had the feel of a hard cord, was exposed. This was dissected free, and removed en masse from the point at which it had previously been ligated, down to and including the extension into the bladder. A piece of tissue about 4 cm. in diameter and the entire thickness of the bladder was removed; the small papilloma in the base of the bladder was also excised. The bladder and prevesical space were



drained separately. Convalescence was satisfactory, and the wound healed promptly.

Examination of the specimen showed that the ureter was about 1.5 cm. in diameter, and that the walls were greatly thickened and infiltrated. The growth at the ureteral meatus seemed to extend on to the bladder mucosa so that the greater part of the tumor seen in the bladder was made up of multiple papillomas prolapsing from the ureter. On opening the ureter it was seen to be almost completely filled with a great many separate papillomas, extending all along the mucosa from the point of the former ligation to and including the bladder mucosa. These tumors were identical, both grossly and microscopically, with

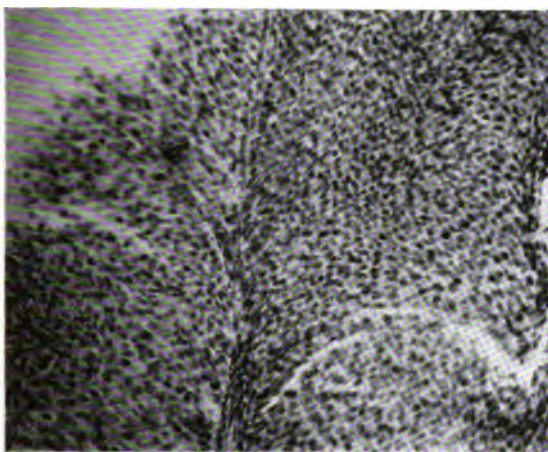


FIG. 107 (235849).—Photomicrograph of squamous-cell papillary tumor of the kidney. The tumor is made up of squamous-cell and slender intervening fibrous stalks.

those removed from the kidney and the ureter more than one year before. The solitary papilloma of the bladder mucosa was of the same structure as those in the kidney and ureter.

The patient is well at the present time, but it is too soon to offer an opinion as to whether or not he will have further trouble. We have advised examinations of the bladder every few months for a period of two years.

CASE 2 (235849).—A man, aged 49, came for examination complaining of pain in the right lumbar region. For a number of years he had had a great deal of pain in his back, but this pain had disappeared about eight years before and he had been free from it until one month



before when it appeared in the right lumbar region. He urinated from three to four times at night, and every two or three hours during the day. His normal weight was 212 pounds; he now weighed 169.

Examination revealed a large tumor in the right kidney region. The hemoglobin was 56 per cent; leukocytes, 31,800. The urine contained pus and red blood cells. X-ray examination showed multiple shadows in the right-kidney region. A diagnosis of right calcareous pyonephrosis was made. Fifty-five per cent phenol-

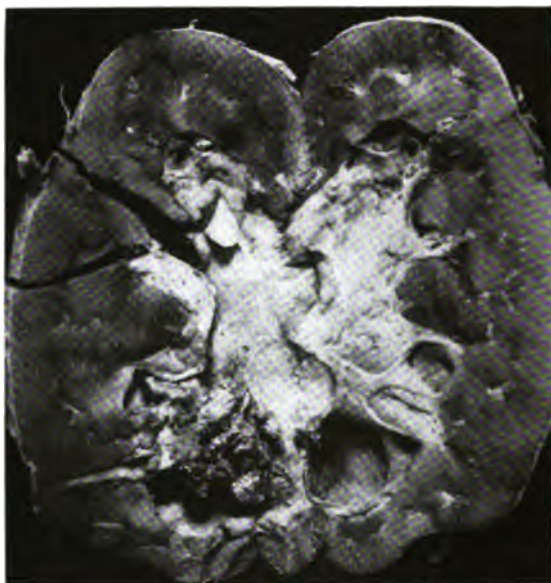


FIG. 108 (103235).—Photograph of papillary adenomatous tumor of the parenchyma of the kidney.

sulphonephthalein was passed in two hours; the function of the right kidney was about half that of the left.

On July 5, 1918, the patient was operated on. The kidney, containing two stones and weighing 950 gms. was removed. Examination of the specimen showed almost complete destruction of the kidney, a papillary carcinoma 8 cm. in diameter, nephrolithiasis, and three stones in the mass. The patient died on the tenth day after the operation. At necropsy metastatic malignancy in the mediastinal lymph glands and also in the lungs was found. The malignancy of the glands was of the type found in the kidney.

Histologically, the tumor was of the squamous-cell papillary type, which probably originated in the pelvis of the kidney; however, this could not be definitely determined because the destruction of the tissue was so advanced. The ureter was not involved (Fig. 107).

In addition to Cases 1 and 2 there were three in which papillary tumors originated in the parenchyma of the kidney. In two it seemed probable that the tumors were secondary to cysts. In all three the growths were so extensive and destructive that it was difficult to be certain of their exact nature; however, in the light of more careful study they appeared to be papillary adenomas.

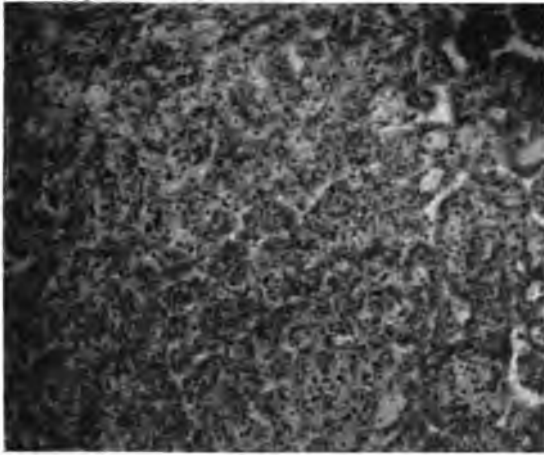


FIG. 109 (103235).—Photomicrograph, of tumor shown in Figure 108.

Fifty-one of the series of 207 cases were of benign tumor, and 34 of these were cysts. One hundred fifty-six cases were of malignant tumor, and 113 of these were classified hypernephromas, 22 carcinomas, and 15 sarcomas.

#### ABSTRACTS OF HISTORIES OF THREE CASES OF PAPILLARY ADENOMATOUS TUMOR OF THE KIDNEY

CASE 3 (34504).—A man, aged 47, had been subject to attacks of colicky pain for from twenty to thirty years. The pain began in the right loin and extended downward. Blood and pus had been noted in the urine. The attacks appeared at intervals of from a few months to four years. Between attacks the patient was well. During the

past two years the pain had been more frequent, and in the past year it was almost constant, especially at night. There was blood in the urine most of the time. The patient had lost weight for several months, and was 40 pounds under weight.

At the time of our examination the patient was somewhat anemic and emaciated. The hemoglobin was 70 per cent. Several small shadows in the right-kidney area were seen in the roentgenogram,



FIG. 110 (141532).—Photomicrograph of papillary adenomatous tumor of the parenchyma of the kidney. The tumor is made up of columnar cells with intervening fibrous stalks.

and a mass which was supposed to be an enlarged kidney could be palpated. Blood and pus were found in the urine, although the amount of blood was not sufficient to be suggestive of a tumor. A diagnosis of right pyonephrosis with stones and a normal left kidney was made.

At operation, March 1, 1910, the enlargement proved to be due to a malignant papillary adenoma of the pelvis of the kidney. The tumor was rather large; stones were present in the pelvis. The patient

made a good immediate recovery from the operation. He died suddenly in July of the same year.

CASE 4 (103235).—A man, aged 29, came for examination complaining of hematuria. Eight years before, following heavy lifting, he had had severe pain for five or six hours, which extended from the right testicle along the right abdomen. Clots of blood were passed; this recurred for a few hours three or four times a year. The patient had had only two attacks of colic, the last one four years before his visit to the clinic. He had had no frequency, urgency, nor burning, but some pain about the neck of the bladder when the clots passed.

The functional test of the kidneys showed a phenolsulphonephthalein return in fifteen minutes, 56 per cent in two hours. A slight amount of albumin, some pus, and red blood cells were found in the urine. Cystoscopic examination showed urine spurting normally from the right meatus, but there was some question as to whether it was absolutely free from blood. The hemoglobin was 84 per cent. A diagnosis of a surgical right kidney was made. The patient went home presumably to arrange his affairs and return for an operation, but he waited three months, at the end of which time he was weak and emaciated, and his hemoglobin had dropped to 44 per cent. Blood had been present in his urine except for short intervals. At operation, July 28, 1914, a small carcinomatous papillary cyst adenoma of the right kidney was found, and the kidney was removed. The renal artery resembled a pipe stem, and very marked hardening of its tissues was noted. The patient made a good immediate recovery, and was discharged in good condition. (Figs. 108 and 109.)

CASE 5 (141532).—A woman, aged 45, came for examination because of "kidney trouble." Her appendix and one ovary had been removed. At intervals during the previous three years she had had hematuria of varying degrees, and had passed clots and also bright red blood. During the last attack, one month before, she passed a teacupful of bright-red blood, and at the same time experienced colicky pain in the right-kidney area. She voided two or three times at night, and had lost 10 pounds in weight in a year.

Examination showed pus and blood in the urine, and an indefinite enlargement in the upper pole of the right kidney. The hemoglobin was 82 per cent. The functional test showed that 20 per cent phenol-sulphonephthalein passed in two hours, and just a trace of blood and no urine coming from the right side. A diagnosis of tumor of the

right kidney was made. At operation, Sept. 28, 1918, the kidney and adrenal gland were removed. The tumor was found to be a carcinomatous papillary cystadenoma. Complete suppression occurred after the operation, and the patient died about the tenth day. Necropsy showed no other evidence of malignancy, although it revealed a marked nephritis in the remaining kidney, a cholecystitis and cholelithiasis, and a hemorrhagic colitis. (Fig. 110.)

#### SUMMARY OF CASE HISTORIES

A brief review of the histories of these 3 cases of papillary adenomatous tumor would seem to indicate that pain in the region of the affected kidney, extending into the loin, is a common accompaniment of renal adenoma, and that patients thus afflicted quickly show emaciation. A palpable tumor was present in all the cases. Blood in the urine is a common symptom in cases of malignant tumor of the kidney, except sarcoma, which occurs almost altogether in children. Blood coming from one kidney should suggest tumor of the kidney. In this connection it is necessary to keep in mind the possibility of tuberculosis, and also those unexplained cases of essential hematuria. The bleeding in our case of papillary tumor of the pelvis of the kidney was different from that which occurred in the three cases of papillary adenomatous tumors. In the first case it occurred in hemorrhages, and the urine was otherwise clean. In the cases of papillary adenomatous tumor a great deal of blood and pus in the urine was a constant finding. The x-ray shadows showed stone, and this led us to think that pyonephrosis and calculi might be present. One point discussed by Cumston in the differential diagnosis is that finding a hematonephrosis in a case in which hemorrhages had been the chief symptom would suggest the presence of a pelvic papilloma. This writer inferred that the papilloma would at times obstruct the ureter, and thus cause a hydronephrosis. It seems to me that a colloidal silver plate made of the pelvis of the kidney in a case of renal papilloma might be quite suggestive, and possibly with the plate a diagnosis could be made; at least a cystogram made of the bladder in which a papilloma exists usually gives a characteristic picture. In our examination, and especially in the treatment of these cases, we must bear in mind the possibility of the existence of a papilloma in the ureter alone which will produce these same symptoms. This lesion is very rare; only a few cases are on record.

## TREATMENT

Nephrectomy is the treatment indicated in cases of squamous-cell papillomas and papillary adenomatous tumors of the kidney if the opposite kidney is in good condition. Conservative treatment of such tumors is almost conclusive evidence that they will recur elsewhere, and it should also be taken into consideration that there is a possibility of an immediate change from a benign to a malignant growth. It would seem almost unnecessary to remove the ureter with the kidney in cases of renal papillary adenomatous tumors when there is no apparent extension into the ureter, but our experience with this one case of squamous-cell papilloma of the pelvis certainly indicates the advisability of always removing the entire ureter down to the wall of the bladder at the time of the nephrectomy, or at a second-stage operation very soon afterward. The most probable point at which broken-off pieces of squamous-cell papillary tumor of the kidney find lodgment is just at the ureterovesical juncture; therefore the best means of cure is to remove the entire ureter.

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## SURGERY OF THE KIDNEY\*

E. S. JUDD

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The improvement and development of the surgery of the kidney have been brought about largely by a better understanding of the pathology, and more by the modern methods of clinical and laboratory examination which have enabled us to determine more accurately than heretofore the existing condition. Very important changes have also been made in the surgical technic.

*Congenital anomalies.*—Some of the congenital anomalies which affect the kidney may have a very important bearing on any surgical procedure. The horseshoe kidney occurs quite frequently, and in certain cases one half of it may be diseased and the other half normal. This condition will often be encountered without any previous knowledge of its presence, and the fact that the two kidneys are fused adds greatly to the difficulties of the removal of the diseased portion. It should also be remembered that one kidney may be imperfectly developed or that there may be a congenital absence of one kidney. These conditions especially call attention to the importance of determining whether or not both kidneys are present and what their functional capacity is before any operation is undertaken. Should it be impossible to make sure at the time of the examination that both kidneys are present and functioning, it may be necessary to explore both sides before deciding to remove the infected kidney. If one kidney is absent or not functioning, the remaining kidney will be twice its normal size.

The kidney may be congenitally displaced, and if so it is usually found at a level with the promontory of the sacrum. This condition is known as pelvic or ectopic kidney and differs from the floating or movable kidney in that the renal vessels may arise from the common or internal iliac vessels and the pedicle of the kidney may be short

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so that it is more or less fixed in the pelvis. A pelvic kidney may be normal in functioning capacity and cause no trouble, or it may be afflicted with any of the pathologic conditions which arise in a normal kidney. A kidney in the pelvis is of great importance from the standpoint of diagnosis. Several times an infected ectopic kidney on the right side has been approached on the presumption that the condition was an appendiceal abscess. It seems advisable to have a pyelogram made in all uncertain cases of pelvic tumor in which an ectopic kidney may be the tumor. In a series of 19 cases of pelvic kidney previously reported 9 of the patients required operation because the kidney was pathologic. In the other 10 cases, the kidney was apparently functioning normally.

The movable and the floating kidney have ceased to occupy an important place in surgery. At one time the surgeon considered it advisable to fix in the normal position all kidneys that seemed to lie too low or to be too movable, but at the present time the mere position of these kidneys is not deemed an indication for operative treatment. Usually, this condition of general visceroptosis is associated with the syndrome of general neurasthenia and will not be benefited by surgery. Undoubtedly, at times the floating kidney assumes a position which causes a change in the position of the ureter, so that the flow of the urine is obstructed and an intermittent hydronephrosis, which can be determined by a special examination, results. In such cases surgical treatment is usually advised, although it does not always obtain the best results. Occasionally, it may seem advisable to fix a floating kidney to relieve symptoms produced by its abnormal position; but more often interference with function is the factor which decides whether or not operation should be done.

*Contusion and rupture of the kidney.*—This injury may occur without any external evidence of trauma over the kidney area. The initial symptom is bloody urine and, if the injury is not extensive, this may subside without further trouble. If the hemorrhage is severe and continuous I believe it is advisable to explore early, in view of the fact that the lacerations may have extended through the pelvis or involved the ureter, and, as a result, the parenchyma will surely become infected, eventually destroying the kidney. In some of these cases, the injury to the vessels, ureter, and pelvis is undoubtedly not so great but that they could be repaired by an early operation which enables the kidney to functionate again. After the infection occurs



in a ruptured kidney the chance of saving it is slight. Nephrectomy will often have to be resorted to in cases of severe injury.

*Hydronephrosis.*—If the escape of the urine from the kidney is suddenly and completely arrested by ligation of the ureter, the organ ceases to secrete, and finally undergoes atrophy. It might be expected that an unfavorable prognosis would follow ligation of the ureter and that eventually the kidney would have to be removed, but in not a single case of the many instances in which we have been obliged to ligate the ureter has a demonstrable hydronephrosis developed, and in no instance has it been necessary to remove the kidney. Experimental work on animals, and Caulk's operative work on the human have demonstrated that if the ureter is liberated after it has been ligated completely and has remained closed for as long as fourteen days, the kidney tissue will gradually recover and functionate normally. Hydronephrosis, then, will not result, from the ligation of the ureter, but it may and usually does result from hindrance to the flow of urine during a long period. The altered position of the kidney or the pressure of an anomalous vessel on the ureter may eventually result in a hydronephrosis. At first the hydronephrosis will be intermittent; later, after changes have occurred in the kidney tissue, especially in the pelvis, the hydronephrosis will become permanent. A small hydronephrosis, with some dilatation of the calices, is not uncommon and may exist without producing symptoms. In view of the fact that surgery is not always satisfactory in these cases it seems best not to be too urgent in advising it. If an anomalous vessel is the cause, the condition will be relieved by the division of this vessel, provided the hydronephrotic sac is not too large. If the cause of the condition is a stricture or an angling of the ureter a plastic operation at this point of the ureter would seem to be indicated. A number of these plastic operations have been done in the clinic in cases in which hydronephrosis was sufficient to produce marked symptoms and yet had not resulted in any destruction of the kidney. The results in these cases have not been generally satisfactory. Some patients have had recurring trouble which required nephrectomy. The operation described by Peck, "splinting the ureter," has proved very satisfactory in some cases. If the hydronephrotic sac is large and the calices markedly dilated, it will be best to resort to a nephrectomy if the other kidney has been found to be normal. Undoubtedly these conditions

are more than a mere dilatation or they would be entirely relieved by a plastic operation at the point of narrowing.

*Pyogenic infections.*—Pyogenic infections of the kidney are common, and in most instances surgical treatment is indicated. If the infection takes the form of a pyelitis or a pyelonephritis, however, both kidneys are usually involved, and little can be accomplished by surgery. A common type of infection in the kidney occurs from several days to several weeks following attacks such as of tonsillitis and boils. The kidney receives the organism through the blood stream and the involvement occurs in the form of a single abscess or, more often, multiple cortical abscesses. This is indicated by chills, a rise in temperature, and a high leukocyte count, and usually by much local pain and tenderness, especially if the infection extends into the perinephritic space. A large perinephritic abscess sometimes forms, drainage of which is frequently sufficient. If multiple abscesses are found in the cortex with considerable destruction of the kidney substance, a nephrectomy is indicated.

Pyonephrosis is that form of infection in the kidney in which supuration is combined with obstruction to the outflow of the urine. This condition may result from infection associated with hydronephrosis or with stones in the pelvis or renal tissue. Bilateral pyonephrosis is frequently encountered in cases of severe cystitis associated with prostatic enlargement and bladder stone. If the pyonephrosis is unilateral, nephrectomy is often advisable. In some cases in which the infection is not severe or in which there is some contra-indication to performing a nephrectomy the kidney pelvis and the kidney tissue may be drained, although under ordinary circumstances the establishment of drainage in an infected kidney is not altogether satisfactory. It is often difficult to decide just how to proceed in cases of bilateral pyonephrosis. Many of these cases are associated with stone formation, and the phenolsulphonephthalein output may be low and the blood urea high. It seems to me that the most conservative method, the removal of stones from one kidney at a time, is best. In occasional cases a subcapsular nephrectomy will be required later because of remaining infection and persistent sinuses, but this can be done at a time when the better kidney has resumed good function. I believe that it is easier for the patient, even in the cases of non-infected bilateral nephrolithiasis, to have one side operated on at a time, the second operation to be performed as soon as complete convalescence has taken

place following the first. Stones in the kidney are most often formed in the pelvis or in one of the calices, although they may occur in the kidney tissue. Calcareous formations in the kidney are frequently multiple; they are ordinarily determined by x-ray examination, but even when the x-ray shows only a single shadow the possibility of a number of stones must be considered. I am convinced that the reported frequency with which kidney stone is found following operation is largely due to the fact that small stones are overlooked at the time of the operation. In operating it is always advisable to deliver the kidney from the wound in order to get good exposure. When it is possible the stone should be removed through an opening in the pelvis, although an incision into the cortex is better handled now than formerly. It is always wise to make an opening in the pelvis large enough, to introduce a finger to explore the calices. This is the best method by which to find stones. It is surprising how large a stone in the kidney may escape notice if the pelvis is not opened and examined from the inside. It has been considered indiscreet to suture these openings in the pelvis or ureter but I believe that this can be done safely with fine, plain, quickly absorbable catgut; certainly the suture adds greatly to the convalescence as in many cases no urine will drain at any time. The contra-indication to closing the kidney pelvis or ureter is the severe infection which may exist.

*Tuberculosis of the kidney.*—Tuberculosis of the kidney is a common finding. In every instance in our cases in which tuberculosis bacilli were found in the urine coming from the ureter, a definite tuberculous process was demonstrated in the kidney. It is of the greatest importance to recognize the condition while the process is confined to a single kidney. When only one kidney is involved, the ultimate results of its removal will be very good, but if the condition has reached the other kidney, no form of treatment is effective. Under ordinary circumstances, if one kidney is extensively involved and the other only slightly, the one showing the greatest destruction should be removed unless there is evidence that the disease is general. Undoubtedly tuberculosis of the kidney is often secondary to tuberculosis of the lungs. A healed lesion in the lung, or a fairly inactive one, is not a contra-indication to removal of a kidney in which an active tuberculosis exists. It adds to the risk, but the operation offers the patient much more than any other treatment (Fig. 111).

In the technic of the removal of a tuberculous kidney, the perirenal

fat must be removed completely and the cut end of the ureter isolated, or the entire wound may become infected and tuberculous with very serious results. Tubercles are found in the tissues of the ureter, and in many cases in the bladder. Removal of the entire ureter has



FIG. 111.—Line of skin incision in kidney cases as previously suggested by W. J. Mayo.

been advocated but this adds greatly to the extent of the wound and does not accomplish its purpose, since a ureter cut off at the bladder offers the same opportunity for soiling as it does when cut off at the kidney pelvis. To prevent infection from the cut end of the ureter

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W. J. Mayo devised the plan of suturing the end of the ureter to the skin so that it prolapses out of the wound. Sometimes it is difficult to free the stiff ureter sufficiently to get it entirely out of the wound

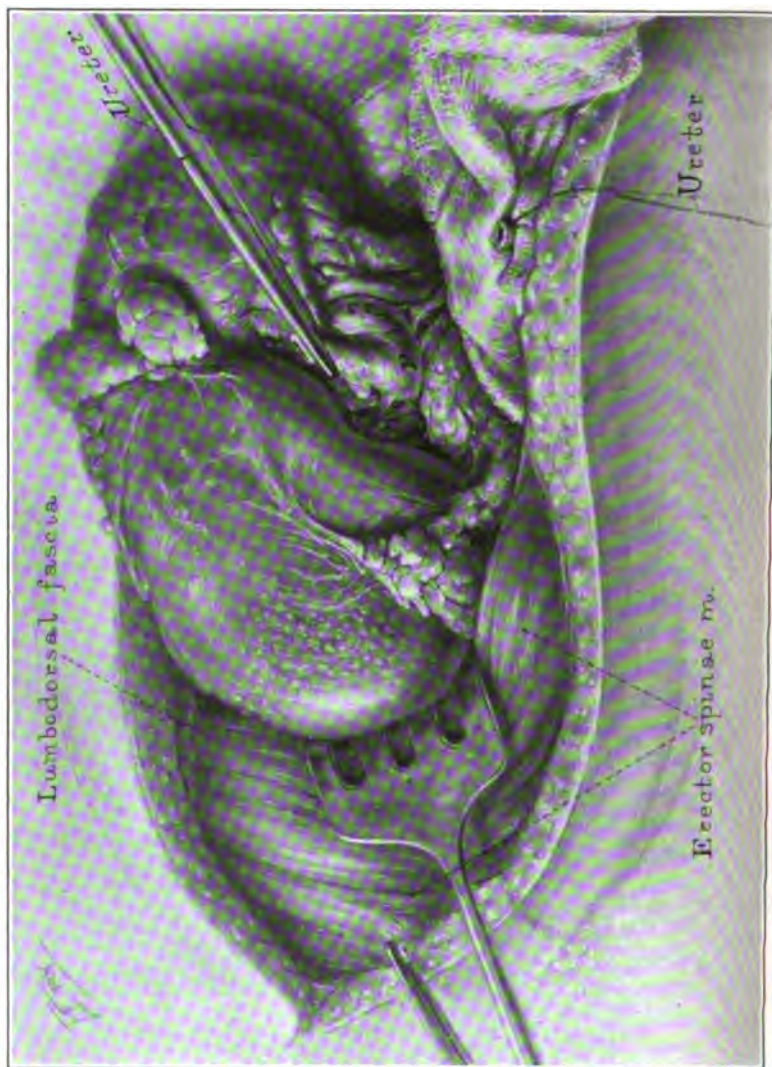


FIG. 112.—Kidney delivered into wound, ureter ligated and dropped back, ready for invagination into tube.

If this cannot be done the end of the ureter is freed for several inches and the ligated end is threaded into a rubber tube, which is allowed to project from the wound for at least six days. In this manner, any soiling from the cut end of the ureter is carried to the outside by the

tube and is not poured into the perirenal tissues. The results following these procedures of isolating the ureter after the nephrectomy for tuberculosis of the kidney indicate their great importance (Figs. 112 and 113).

*Tumors of the kidney.*—A study of renal tumors shows benign tumors of the kidney to be very rare. Solitary cysts that may be

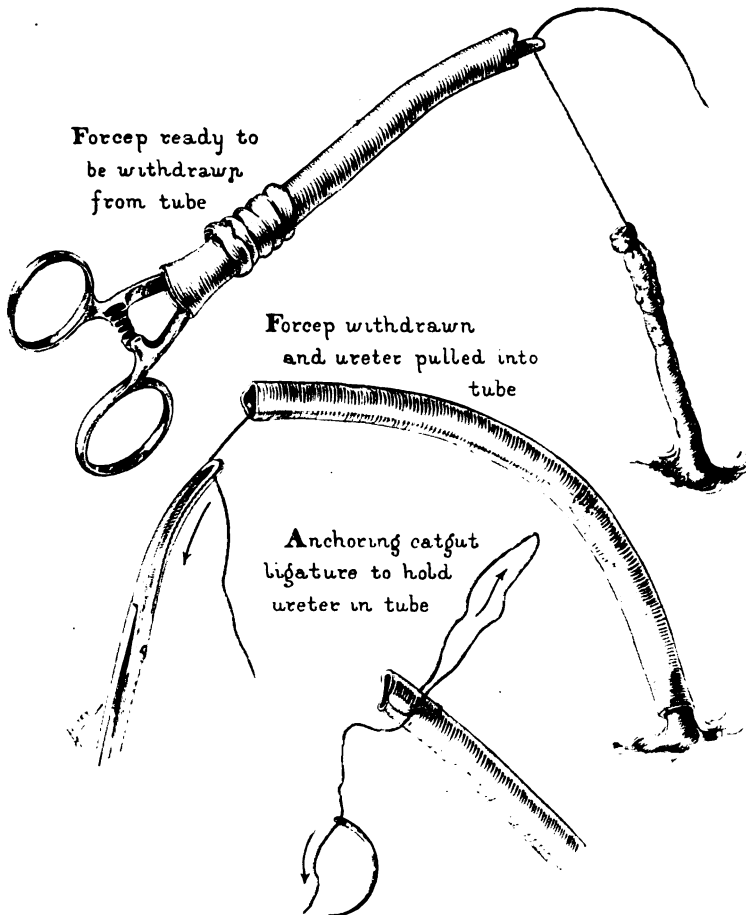


FIG. 113.—Method of isolating cut off area of a tuberculous ureter.

enucleated from the kidney are sometimes seen. Congenital, bilateral polycystic disease is more common, but it is not particularly amenable to surgical treatment. Patients are usually very anemic and have a low kidney function. If one of the cystic kidneys is also infected and the other is free from infection, it is sometimes advisable

to remove the infected organ. Our experience with the Rovsing operation, which consists in collapsing the cysts in first one kidney and then the other, has not been entirely satisfactory. The common tumors of the kidney are malignant, either hypernephroma or carcinoma in the adult, or sarcoma in children.\* The results of nephrectomy for hypernephroma have been more permanent than those of most operations for malignancy. The tumor develops slowly and, if operated on before it becomes fixed by attachments formed from extension, especially through the pedicle and extensive lymphatic involvement, the results are very satisfactory. If the tumor is large and fixed no operation should be attempted, and it may be well to

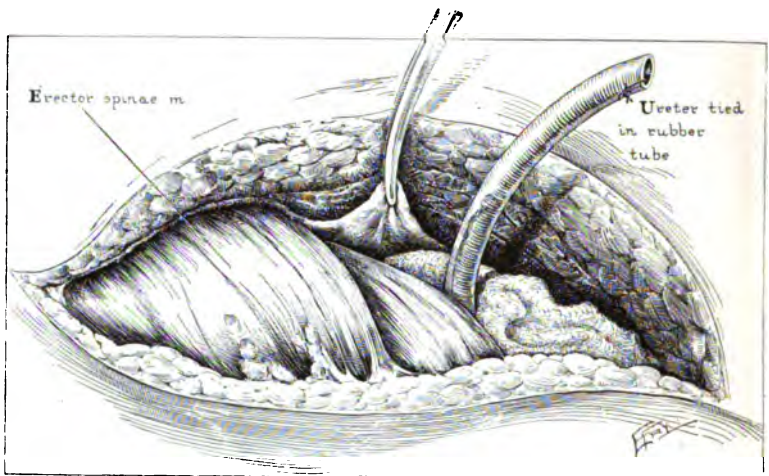


FIG. 114.—Tuberculous ureter fastened in rubber tube isolating it from the surrounding tissues to prevent soiling.

use radium. Some of our patients with inoperable tumors who otherwise were in fair condition have seemed to do very well under this treatment. Operation for carcinoma and for sarcoma of the kidney in children is less favorable; while a very large tumor may be removed successfully it will usually recur early (Fig. 114).

*The technic of operation.*—I wish to call your attention to the incision which we have found most useful in exposing the kidney. This was described by W. J. Mayo some years ago (Fig. 111). It combines the advantages of the so-called posterior and anterior incisions, adding materially to the facility with which these operations may be performed. It is crescentic, beginning well forward on the

flank above the spine of the pubic bone, extending backward and upward to the point of articulation between the last rib and the vertebræ. The incision must extend far enough forward to give a good exposure of the pedicle in cases in which the pedicle is short and the kidney high-lying. The operation is extraperitoneal throughout. The important sensory nerves come into view readily and are preserved. In some instances it is necessary to cut through the muscles. Second, the perirenal fat should be extensively removed in all tuberculous and malignant cases. Third, the cut-off end of the ureter should be isolated in all tuberculous cases in such a manner that it will not soil the wound. This may be accomplished by fastening the ureter outside the wound or isolating it by threading it through a rubber tube. Fourth, the pedicle consisting of the renal vessels should be caught by two clamps. When tying the pedicle the deeper of the two clamps is released while the ligature is being tightened onto the pedicle; in this way the pedicle is controlled by the ligature and by the second clamp. Another ligature is then placed on the pedicle before the second clamp is removed.

TABLE 1.—OPERATIONS ON THE KIDNEY IN 1918

	Cases	Deaths
Perinephritic abscess—drainage.....	7	
Anomalous kidney—exploratory pelviotomy.....	1	
Carcinoma of the kidney—exploration.....	2	1
Cysts of the kidney—exploration.....	1	
Cysts of the kidney—Rovsing operation.....	2	
Cystadenoma—enucleation.....	1	
Hematuria—nephrotomy.....	1	
Hydronephrosis and ureteral calculi—nephro-ureterectomy.....	1	
Hydronephrosis and hydro-ureter—nephro-ureterectomy.....	2	
Hydronephrosis (intermittent)—Peck's operation.....	2	
Plastic operation and division of blood vessels.....	4	
Hypernephroma—exploration.....	3	
Inoperable malignancy, tuberculosis, both kidneys diseased—exploration.....	12	
Movable kidney—decortication and nephrorrhaphy....	2	
Nephrolithiasis—nephrolithotomy and pelviolithotomy.	86	2
Nephrectomy (partial).....	6	
Edebohls' operation.....	2	1
Pyonephrosis and pyo-ureter—nephro-ureterectomy....	5	
Acute suppression—decortication.....	4	2
Papillitis—nephrotomy.....	2	
Tuberculosis—nephro-ureterectomy.....	3	
Sinus dilatation and curettage.....	1	



The points to be emphasized in operations for the removal of stones from the kidney are, first, exposure of the kidney by displacing it from the wound; second, careful exploration of the kidney pelvis and calices with the finger in order to avoid overlooking any stones; and third, closure of the incision in the kidney pelvis in non-infected cases.

TABLE 2.—OPERATIONS ON THE KIDNEY IN 1918

	Cases	Deaths
Nephrectomy.....		239
Tuberculosis of the kidney.....	81	
Pyonephrosis (associated with nephrolithiasis, 34)....	67	
Hydronephrosis (associated with nephrolithiasis, 6)...	41	
Tumor of the kidney.....		
Hypernephroma.....	18	
Carcinoma.....	3	
Sarcoma.....	1	
Pyelonephritis.....	9	
Polycystic kidney.....	3	
Nephrolithiasis with multiple cortical abscesses....	2	
Multiple cysts and abscesses.....	2	
Remnant of kidney following operation elsewhere....	2	
Congenital cystic kidney.....	1	
Retroperitoneal sarcoma adherent to kidney.....	1	
Multiple abscesses of the kidney.....	1	
Pyelitis.....	1	
Infected atrophic kidney.....	1	
Recurring stones with sand.....	1	
Ruptured kidney—perinephritic abscess.....	1	
Branched stone with kidney substance destroyed....	1	
Nephrolithiasis—chronic nephritis.....	1	
Chronic infection.....	1	

## SURGICAL MORTALITY

Of the 239 patients on whom nephrectomy was done 7 (2.9 per cent) died. Three had tuberculosis of the kidney; one died of tuberculous bronchopneumonia, one of miliary tuberculosis of the lungs and tuberculous peritonitis, and one of chronic nephritis and bilateral pleuritis. Two of the patients had pyonephrosis; one died of hemorrhage (forceps on pedicle) and one of thrombophlebitis of the inferior vena cava, the common, internal, and external iliac veins. One patient with hypernephroma died of an infection. This patient was operated by the transperitoneal route. One patient with carcinoma of the kidney died of acute nephritis and metastatic carcinoma in the lungs.

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## DILATATION OF THE URETER AND RENAL PELVIS\*

W. F. BRAASCH

Dilatation of the ureter and renal pelvis may be caused by these etiologic factors: mechanical obstruction, infection, and disturbance of innervation. The various types may be recognized by differences in (1) outline, as observed in the pyelo-ureterogram, (2) pathology, and (3) clinical data.

### MECHANICAL OBSTRUCTION

Continued mechanical obstruction in any portion of the urinary tract is necessarily followed by dilatation of the portion above it. It may be conceivable that an occasional obstruction may cause urinary retention of such short duration that no dilatation in the ureter or pelvis would be apparent; but in the presence of a more or less permanent obstruction causing urinary retention, it would be impossible not to have a visible permanent distention of the ureter and the renal pelvis.

*Pelvis.*—Dilatation in the pelvis caused by mechanical obstruction is usually characterized by (1) predominance of dilatation in the pelvis rather than in the calices or ureter, and (2) comparative regularity of pelvic outline.

The various changes in the pelvic outline resulting from mechanical obstruction are best described by considering them according to degree. As demonstrated by the pyelogram, the following deviations from the normal pelvic outline may be noted:

1. Early hydronephrosis: (a) flattening of terminal irregularities; (b) broadening of the base of the calix; (c) increase in size of the true pelvis, and (d) shortening of papillæ.

2. Moderate hydronephrosis: (a) broadening of the entire calix; (b) shortening of papillæ; (c) change in the angle of insertion of the

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ureter; (d) increase in size of the pelvis, and (e) changes of secondary infection.

3. Large hydronephrosis: (a) partially filled calices; (b) rounded individual areas; (c) single calices; (d) diffuse outline of rounded sac, and (e) dim areas suggestive of diluted opaque fluid.

*Early hydronephrosis.*—Probably the first deviation from the normal to be noted in the pyelogram with early hydronephrosis is a flattening of the terminal irregularities of the normal minor calices, together with a slight broadening of the major calix. Immediately following or accompanying these changes may be noted an increase in the size of the true pelvis. With the increase in the size of the pelvis, a shortening or flattening of the papillæ projecting between the major calices may be noted.

*Moderate hydronephrosis.*—With further increase in size of the hydronephrosis, the major calix becomes considerably broader in its entire extent, as well as shorter, while the terminal irregularities will usually have been effaced. The abbreviation of the calix may proceed to such an extent that one or two irregular indentations in the otherwise rounded contour of the true pelvis may alone remain. Accompanying these changes in the outline of the calix, a marked increase in the size of the true pelvis will usually occur. The pelvic outline is usually even and well rounded along its free border; this is typical of mechanical distention. Its size now makes it easily distinguishable from a large, normal pelvis. This increase in size of the true pelvis may be out of proportion to the more moderate changes seen in the calices. With the increase in size of the true pelvis, the papillæ which normally project between the major calices well into the pelvic lumen, become distinctly shorter and may become so flattened as practically to be effaced.

*Large hydronephrosis.*—It will usually be difficult to demonstrate the entire contour of a greatly distended pelvis in the pyelogram because of the dilution of the injected medium by the retained fluid. The pelvis is now a large round sac, with rounded calices extending from it. The calices alone may be visible and appear as detached, irregularly rounded areas, particularly when partially filled.

*The ureter.*—Dilatation of the ureter because of mechanical obstruction is characterized by an increase in the size of the lumen and by thinning of the ureteral wall. The degree of dilatation is greatest near the point of obstruction, and diminishes gradually as it

nears the pelvis. This is in marked distinction to the inflammatory dilatation, which is often greatest at the ureteropelvic juncture and smaller in its lower portion. The degree of dilatation accompanying

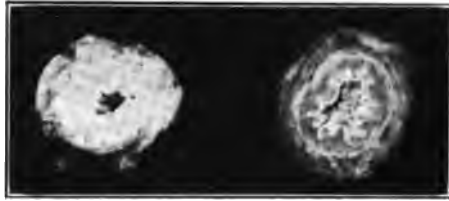


FIG. 115 (244137).—Cross section of ureter with chronic ureteritis. Note thickening of wall and dilatation of lumen.

mechanical obstruction is usually greater than that resulting from infection.



FIG. 116 (224202).—Microscopic section showing increase in size of lumen, leukocytic infiltration of submucosa and cicatricial changes in serosa. Comparative diminution of muscle fibers.

A stricture of the ureter may occur which obstructs the ureteral lumen only temporarily,<sup>2</sup> and it is possible that the ordinary method

of cystoscopic examination may fail to disclose the presence of such a stricture, when examination is made during the interval of patency. A ureterogram may be of considerable value in such cases and may be the only method by which the condition can be demonstrated. Further, even though the existence of a stricture is ascertained by means of the ureteral catheter alone, its extent and the degree of dilatation above it can frequently be ascertained more accurately by means of the pyelo-ureterogram. When encountering an obstruction to the ureteral catheter, considerable difficulty may arise in differentiating an anatomic and a pathologic condition. The catheter may meet an obstruction at any level of the ureter, as the result of some anatomic condition, such as acute angulation in the course of the ureter, marked elasticity of the ureteral wall, or a loose mesenteric attachment. With most anatomic obstructions, an injected fluid will pass any obstruction offered to the ureteral catheter, and the absence of dilatation or any evidence of abnormality will demonstrate the anatomic nature of the obstruction. With a pathologic obstruction, when the fluid gets by, a nodular dilatation about the obstruction or a diffuse dilatation of the ureter is visible.

#### INFLAMMATORY DILATATION

Any considerable degree of chronic infection involving the renal pelvis and ureter will be followed by dilatation. This dilatation is not caused by a mechanical obstruction, but is the result of either a change in the tissues, and a consequent retraction in the walls of the pelvis and ureter, or of necrosis. The dilatation may vary from scarcely recognizable irregularity of the calices or dilatation of the ureter to complete destruction of the pelvis.

*The pelvis.*—Dilatation of the renal pelvis as the result of inflammatory changes in its walls differs from mechanical dilatation largely in these characteristics: (1) predominance of dilatation in the calices or ureter rather than in the true pelvis, and (2) comparative irregularity of outline. It will be found that certain renal infections (evidently those predominant in the tissues adjacent to the renal pelvis) are usually accompanied by a considerable degree of inflammatory dilatation largely in the calices, whereas, in the other renal infections (evidently those predominant in the renal parenchyma), the dilatation is confined to the ureter, with an actual decrease in the

size of the pelvis. The changes more commonly found in the outline of the renal pelvis as the result of an inflammatory process are: (1) dilatation confined largely to the calices; (2) dilatation involving the entire pelvis; (3) pyonephrosis; (4) contraction of the pelvis with the dilatation of the ureter; (5) alternating contraction and dilatation, and (6) atrophy.

*Dilatation predominant in the calices.*—The earliest changes in the pelvic outline, as a result of infection, are commonly characterized by a slight broadening and irregular rounding or “clubbing” of the calices, with scarcely recognizable changes in the true pelvis. As the inflammatory process progresses, the dilatation in the calices may become well marked, while little or no dilatation may be apparent in the true pelvis. Marked dilatation of the upper ureter, particularly



FIG. 117 (25012).—Cross section of tuberculous ureter. Specimen hardened; actual size of ureteral lumen not apparent.

at the ureteropelvic juncture, is commonly seen with dilatation in the calices.

*Dilatation involving the entire pelvis.*—With inflammation of long duration, dilatation of the true pelvis to a variable degree may also result. This occurs secondary to the dilatation in the calices, and is continuous with that in the ureter.

*Inflammatory contraction of the renal pelvis.*—A decrease in the size of the pelvic outline frequently accompanies infection, which is largely confined to the renal parenchyma, involving the pelvis and ureter secondarily. The pelvis may appear markedly contracted, with narrow slits representing the calices.

*Destruction of pelvic outline, or pyonephrosis.*—With the extension of the inflammatory process and consequent destruction of the normal outline of the calices, the cortex may be invaded, and the resulting areas of necrosis may merge with the calices. The areas of cortical destruction which extend beyond the calices may be connected by

narrow isthmuses with the apexes, so as to give a very irregular outline to the pelvis.

*Alternating contraction and dilatation.*—With a chronic inflammatory process largely confined to the renal pelvis, its outline may become irregularly contracted as well as dilated. This may be due either to contraction as the result of inflammatory changes in the peripelvic tissues, or to encroachment on the lumen by inflammatory proliferation of the pelvic mucosa.

*Atrophic contraction of the pelvis.*—An atrophic condition of one or of both kidneys is occasionally observed. Microscopic examination

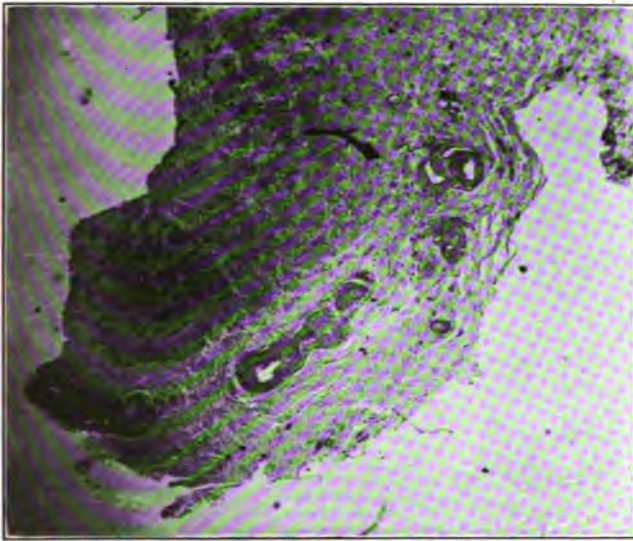


FIG. 118 (25012).—Microscopic section of tuberculous ureter, showing round-cell infiltration of submucosa and cicatricial changes in serosa.

of the renal tissue often demonstrates the existence of an etiologic inflammatory process. The resulting cicatricial changes may cause diminution in the size of the pelvis commensurate with the decrease in parenchyma.

Inflammatory dilatation of the renal pelvis frequently accompanies renal stone, and may be of diagnostic value. The typical clubbing of the calices, with little or no dilatation of the pelvis or ureter, is frequently observed. That the stone could not cause mechanical obstruction is evident from the fact that the stone may be securely lodged at



the end of a calix. Such dilatation may be of definite value in interpreting the identity of a small shadow in the renal area.

*The ureter.*—As with inflammatory changes in the renal pelvis, an inflammatory process in the ureter is followed by tissue changes in its walls which cause more or less dilatation. The changes in the pelvic outline may be so slight as to remain unrecognized, whereas the dilatation in the ureter may be the only evidence of a previously existing inflammatory process. The outline of the ureter, if well distended with mediums, will appear dilated as the result of infection. This dilatation

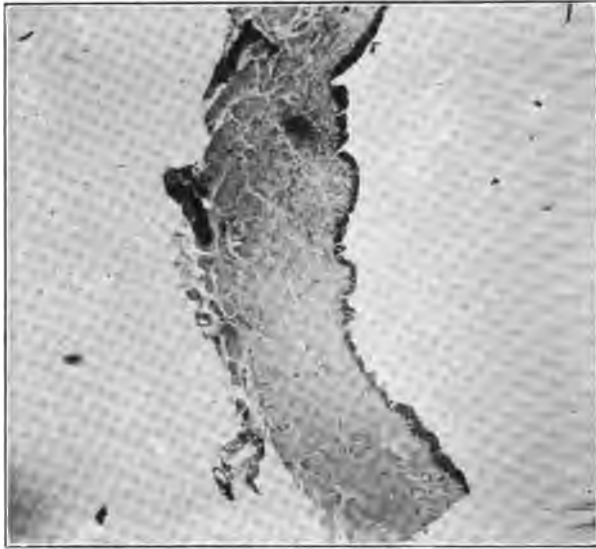


FIG. 119 (181497).—Mechanical dilatation. Microscopic section of a ureter dilated by a stricture. Note thinning of section of serosa and submucosa with comparative hypertrophy of musculature.

is usually greatest near the ureteropelvic juncture, in contrast to the dilatation resulting from stricture of the lower ureter, which is usually greatest near the point of constriction. The ureter, particularly in its upper portion, is frequently tortuous, and occasionally appears markedly angulated.

The portion of the ureter situated in the wall of the bladder will not become so dilated as the portion of the ureter above, unless the bladder itself is markedly inflamed. Dilatation of this portion of the ureter is the result of contiguous infection and is usually observed only with marked chronic infection of the bladder wall. On cysto-

scopic examination, no contraction of the dilated meatus may be visible, which would lead one to believe that with the alteration of tissue in the ureteral wall peristalsis is absent. Such dilatation may often be demonstrated by filling the bladder with an opaque solution and placing the patient in the Trendelenburg position, thus permitting the fluid to enter the ureter by gravity. This method will usually be found impossible unless the ureter in the wall of the bladder is dilated, since the contraction of the meatus and ureteric peristalsis would otherwise prevent the fluid from entering the ureter. Regurgitation of



FIG. 120 (260776).—Typical inflammatory dilatation. Note distention of calices. Pelvis small.

bladder fluid into the ureter, ascribed to insufficiency of the ureteral valve, has been noted by Hagner, Kretschmer and others. Hagner surmised that this was the result of inflammatory changes in the bladder wall.

Ureteral dilatation is frequently observed with prostatic obstruction, and is usually ascribed to the result of mechanical distention. While this may be true in most cases, considerable ureteral dilatation has been observed in which the retention never was greater than

approximately 50 c.c. This usually occurs in the presence of a variable degree of chronic pyelonephritis, which is evidently the etiologic factor.

*Combined inflammatory and mechanical dilatation.*—It must, of course, be considered that both inflammatory and mechanical factors may be present with ureteral and pelvic dilatation. Either factor may be the primary cause of dilatation with secondary influence of the other. Thus, a primary inflammatory dilatation, such as occurs with chronic pyelonephritis, may be complicated by a stricture



FIG. 121 (230063).—Inflammatory dilatation, with cortical infection characterized by a decrease in the size of the pelvis and calices, and by a dilatation of the ureter.

formation, with the usually subjective symptoms of urinary retention. Likewise, a primary stricture of the ureter will sooner or later cause urinary infection, together with an inflammatory invasion of the ureteral wall. In fact, it may be difficult to determine which was the primary factor.

*Pathology of the inflamed pelvis and ureter.*—The frequency with which dilatation of the ureter and pelvis is observed at necropsy, when no evidence of mechanical obstruction can be found, has been noted by various observers.<sup>11</sup> With chronic infection of the pelvis

and the ureter, a change takes place in their tissues which is evidently the cause of dilatation. When the pelvis is opened, the calices are usually dilated to a variable degree, and the pelvic wall is thickened. When dilatation of the true pelvis is present, it is not so great as that usually seen with mechanical obstruction to the ureter, nor is there such thinning of the walls. On inspection, the increase in size of the ureter is found to vary from a slight degree to a diameter of 2 cm. Dilatation to a greater degree than this is usually the result of mechan-

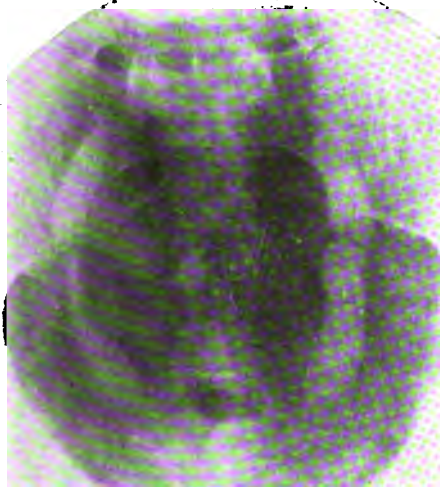


FIG. 122 (117716).—Atonic dilatation of the ureters resulting from lesion of the central nervous system.

ical obstruction. On palpation, the ureter is discovered to be thicker than normal and firmer. This is particularly so with renal tuberculosis. On cross section of the ureter, the walls are seen to be hypertrophied, and the lumen is increased in proportion. With some cases of infection, the changes found in the ureter may be greater than those visible in the pelvis. A microscopic examination of the walls of the pelvis and the ureter reveals the abnormalities: (1) proliferation and often cornification of the mucosa; (2) a variable degree of leukocytic infiltration of the submucosa and musculature; (3) a variable degree of

connective tissue change in the submucosa and serosa, and (4) a relative thickening, often to a marked degree, of the serosa. In the main, the inflammatory changes differ from the mechanical in (1) the greater degree of leukocytic infiltration; (2) in more marked connective tissue changes in the submucosa and serosa, and (3) in increase in thickness of the serosa.

*Data with renal tuberculosis.*—Of particular interest is the dilatation which may occur with renal tuberculosis. The cystoscopic picture of a gaping, dilated meatus, with marked inflammation around it, while the other meatus is quite normal in its aspect, is familiar to us all in the classical picture seen with unilateral renal tuberculosis. The bladder in this condition is usually contracted, and the possibility of any mechanical obstruction in the urethra can usually be excluded, particularly when the condition occurs in the female. If a nephro-ureterectomy is made, the ureter is usually found with one or more strictures above the bladder wall. Occasionally, however, it may be found to be dilated throughout its entire extent, with absolutely no semblance of a constriction in any portion. The pelvis is often found to be slightly dilated; the calices to a variable degree, some very markedly, and some extending into the necrotic cortical areas. It would appear that any possibility of mechanical obstruction could be absolutely excluded, and yet there is a dilatation which remains to be accounted for. On microscopic examination, the walls of the ureter may fail to disclose any particular point of cicatricial narrowing, but will have the typical tissue changes seen with inflammatory reaction.

#### ATONIC DILATATION

Dilatation of the ureteral meatus, associated with paralysis of the bladder resulting from disease in the nervous system, was described by Koll. Such a dilatation occurs with only a small proportion of so-called "cord bladders." The dilatation of the ureter is not confined to the lower end, however, but may extend to the renal pelvis. Such a dilatation may in some instances be due to backing of the urine from the over-distended bladder; atonic ureteral dilatation may be found, however, when no residual urine is present. It is more probable that the same disturbance of innervation of the bladder also affects the ureter, particularly in its lower portion. With the relaxation of the bladder musculature, as frequently occurs with

spinal cord disease, the ureter may relax to a proportional extent. That such a dilatation may involve the entire ureter can occasionally be demonstrated by a cysto-ureterogram.

Another form of dilatation involving the ureter and pelvis has been described by Fedorow, Israel, Bachrach, Buerger, Kretschmer and others, a form in which no definite etiologic factor is evident. Neither mechanical obstruction, evidence of infection, nor disease of the central nervous system may be present. The ureteral meatus is gaping, the entire ureter dilated to a marked extent, and a variable degree of hydro-



FIG. 123 (8886).—Typical mechanical dilatation. Note the large size of the true pelvis in proportion to the size of the calices.

nephrosis may exist. This condition is usually bilateral, and has been variously ascribed to atony (Fedorow), spasmodic contracture of the bladder (Israel), inflammatory dilatation (Karaffa-Korbutt), and congenital insufficiency of the ureteral sphincter (Bachrach). While the various authors differ widely with regard to the etiologic factor, they are all agreed in stating that no stricture can be demonstrated. We have observed 5 such cases at the Mayo Clinic, and the condition was bilateral in all. One of the patients died following a cysto-ureteropyelogram, the medium used being collargol. On postmortem,

both ureters were found to be dilated throughout, and the kidneys were hydronephrotic. No evidence of mechanical obstruction was evident in any portion of the urinary tract, nor was there any clinical evidence of disease involving the central nervous system.

Congenital stricture is such a rarity as to be an almost negligible factor. It is probable, furthermore, that many cases of dilatation reported as due to congenital stricture are really the result of an acquired mechanical obstruction.

#### CLINICAL DATA

When viewed from a clinical standpoint, the subjective data accompanying mechanical and inflammatory dilatation are quite distinct. It is difficult to conceive that there may be, without the presence of pain, an intermittent mechanical obstruction, with consequent overdistention of the pelvis and ureter by the retained urine. In the majority of cases the degree of pain is usually great, although it may be conceivable that with partial obstruction it might be of a moderate character. However, if the obstruction is sufficient to cause any marked degree of dilatation, the pain will be severe. With the dilatation such as is so frequently seen with chronic pyelonephritis, however, there is usually little or no pain referred to the kidney. We have repeatedly demonstrated marked dilatation, particularly of the ureter, which we regard as due to inflammatory causes, when the patient has complained of no pain whatever. In reviewing 240 cases of pyelonephritis, Thomas found that pain was present in less than 20 per cent. If a history of definite pain is given, we have been led to believe that there must be some complicating mechanical obstruction.

#### CONCLUSIONS

1. Dilatation of the ureter and renal pelvis may occur without mechanical obstruction.
2. The differences between mechanical and inflammatory dilatation, in their anatomy and pathology and in clinical data, are quite definite.
3. The clinical demonstration of inflammatory dilatation may be of diagnostic value.

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## CONDITIONS CONTRA-INDICATING OPERATION WITH STONE IN THE KIDNEY AND URETER \*

W. F. BRAASCH

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Methods of diagnosis and localization of renal stones have been developed to such a degree of accuracy in recent years that the percentage of error has been reduced to a minimum. When the diagnosis is established it is frequently of equal importance to determine the advisability of operation. Several circumstances should be considered before operation is recommended. Among the most important of these are: (1) duration of symptoms; (2) size; (3) situation; (4) number of stones; (5) certain types of bilateral lithiasis; (6) low renal function; and (7) complications in other organs.

*Duration of symptoms.*—The duration of symptoms should be a considerable factor in determining the advisability of immediate operation. It is not generally realized that probably 75 per cent of renal stones pass spontaneously. The majority of these stones will probably pass within three or four months following the first symptom. It may be stated, therefore, that it is usually inadvisable to operate for a stone in either the kidney or ureter until at least three months, and possibly six months, have elapsed since the onset of the symptoms. Immediate operation for stone following the first or second attack of pain, without evidence of other complications, is strongly to be condemned. Nature should be given full opportunity to remove the stone without intervention. There may be exceptions to this rule, of course, such as excessive pain continued over several weeks or months; evidence of acute cortical or perinephritic infection; and evidence of urinary retention sufficient to endanger the kidney. Moreover, when it is evident that the stone is too large to pass nothing is gained by further delay even though the onset of symptoms is very recent.

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*Size of stones.*—When the roentgenogram shows the stone to be less than 2 cm. in diameter, operation should be delayed in the hope of subsequent passage. When the stone is situated in the kidney and is less than 2 cm. in diameter, it may be very difficult to find at operation, and the search may cause considerable destruction of renal tissue. The difficulty of search is increased and consequent destruction of tissue is greater when multiple small stones are present, even though the diagnosis is evident. When the symptoms are indefinite and the identification of the shadow uncertain, immediate operation should not be considered. When the symptoms are not too severe, and there is but little evidence of renal infection, it is advisable to defer operation until the stone has increased in size.

*Situation.*—Stones situated in the renal cortex or in the end of the calices as a rule cause less damage to the kidney substance, and produce less acute symptoms than stones situated in the pelvis. As a rule the urgency for operation for a stone in this situation is, therefore, not so great. When a stone is situated in the lower ureter, every opportunity should be given for spontaneous passage unless previously mentioned complications are present. Repeated x-rays, taken at intervals, which show a change in position of the stone are indicative of its early passage. When the stone is situated in the bladder portion the possibility of its passage, naturally, is increased. Rarely is an operation indicated when a small stone is situated so as partially to protrude from the meatus.

*Number of stones.*—When the roentgenogram shows the existence of more than one stone in the kidney or ureter, even though they are of a size which may pass spontaneously, it is usually advisable to operate. Conditions permitting the formation of multiple stones are usually surgical, and the time elapsing before spontaneous passage of such stones may permit of considerable renal damage. If one stone is situated in the ureter and the other in the kidney pelvis, if the stone in the ureter is larger, and efforts to remove it without operation have been unavailing, operation on the ureteral stone is indicated. If the renal stone which remains is less than 2 cm. in diameter, operation should be delayed in order to give the opportunity for the stone to pass spontaneously.

*Bilateral nephrolithiasis.*—In the course of routine examinations stones will be found in both kidneys in approximately every sixth person suffering with renal lithiasis. Although surgical treatment

is usually advisable, conditions may be such that any operation for bilateral nephrolithiasis is definitely contra-indicated. When there are no acute symptoms and when the stones in both kidneys are very large and multiple operation is usually inadvisable. Removal of such stones situated in both kidneys is usually accompanied by considerable destruction of the kidney tissue, and the chances are that the patient would live as long and as comfortably without operation. When the symptoms are acute and unilateral, however, operation is of course indicated.

*Renal function.*—Clinical and laboratory evidence of a very low renal function should usually contra-indicate operation when the symptoms are not very acute or persistent. Operation may be justifiable with acute symptoms, however, even though the renal function is far below the normal. It is surprising how well patients with a functional test of less than 20 per cent phenolsulphonaphthalein will react following the removal of a renal stone. Furthermore, a renal functional test of from 20 to 30 per cent in the presence of lithiasis, particularly when bilateral, will frequently become approximately normal after the stones have been removed. When the phenolsulphonaphthalein return is only a trace, however, and the urea retention is high, operation should not be considered unless the symptoms are urgent. Renal stone occurring with chronic nephritis is observed occasionally. The removal of such a stone will usually not affect the course of the primary nephritis and, unless the surgical indications are urgent, operation is inadvisable. Stone occurring with bilateral pyelonephritis, however, should be removed even though the symptoms are not urgent. Removal of such stones will usually have a favorable effect in that it tends to diminish the infection and further the benefit derived from pelvic lavage. It is advisable to ascertain the function of the opposite kidney before operating for renal stone, since the necessity for nephrectomy may be found on exploration. When the opposite kidney is practically functionless or when it is absent a conservative operation is necessary. Operation for stone in polycystic kidney has been done in the Mayo Clinic in 5 cases. Although operation on a polycystic kidney is usually inadvisable, acute symptoms caused by the secondary formation of stone may necessitate surgical relief. Nephrectomy is indicated only when a complicating infection has rendered the affected kidney functionless. A careful estimate of the comparative renal function is indispensable in cases

of polycystic kidney. When glycosuria is present, the same precautions should be observed which are necessary in surgery in any other portion of the body, that is, the reduction of sugar by dietary and other means, and operation only when absolutely necessary.

*Coincident disease.*—Lesions in other organs are frequently noted coincident with renal lithiasis and they may influence the advisability of operation. The presence of a coincident lesion may bring up the question of which lesion should have precedence in treatment. When the several conditions are surgical the lesion which causes the most acute symptoms naturally necessitates operation first. In the long list of coincident diseases, lesions in the alimentary tract and renal lithiasis are the most common. Surgical lesions in the gall-bladder, appendix, and duodenum coincident with renal lithiasis occurred in more than 10 per cent of the patients operated on in the Mayo Clinic. The coincident lesion may be such that operation on the kidney should be postponed or even permanently contra-indicated. Certain forms of cardiac diseases when advanced may render such an operation inadvisable even though no evidence of decompensation may be present at the time. This is particularly true in the aged. It is not to be inferred, however, that cardiac lesions which are well compensated or of moderate degree will offer any contra-indication to renal operation.

Hypertrophy of the prostate gland coincident with renal lithiasis is occasionally observed. In cases in which most of the symptoms are caused by the prostatic obstruction, prostatectomy is indicated after the usual course of preparation, provided that the other kidney is normal. When the renal symptoms are so acute as to require primary operation the degree of urinary retention is of considerable importance. When a large amount of residual urine is present a preliminary drainage and its usual reaction should precede the renal operation if possible.

Pregnancy, particularly of less than six months, offers no contra-indication to operation. If the symptoms become acute and persistent it may be necessary to operate as an emergency measure even in the later months. As a rule, however, in the latter period of pregnancy it is advisable to defer any operation. Unilateral lithiasis should not cause any serious complication during the course of pregnancy or labor. With bilateral nephrolithiasis, however, renal insufficiency may interfere to such an extent that induced labor may be necessary.

During the years 1917 and 1918, 79 cases were diagnosed renal

lithiasis at the clinic in which operation was not advised. In this group the various causes assigned were as follows:

	Cases
Operation deferred because of indefinite diagnosis either from clinical or roentgenographic and cystoscopic data.....	43
Lesions of the central nervous system.....	1
Advanced pregnancy.....	2
Bilateral nephrolithiasis with evidence of uremia.....	3
Hypertrophy of the prostate with renal insufficiency.....	3
Excessive adiposis with indefinite symptoms.....	1
Advanced age.....	2
Advanced malignancy in other tissues.....	2
Advanced disease in the other kidney; renal insufficiency.....	1
Advanced bilateral pyelonephritis.....	2
Advanced cardiac disease.....	6
Chronic nephritis.....	2
Hypernephroma of the opposite kidney.....	1
Bilateral nephrolithiasis with pregnancy.....	1
Myocardial disease and goiter.....	1
Active lues.....	2
Advanced diabetes.....	1
Bilateral pyonephrosis.....	1
Single kidney with indefinite shadow.....	1
Active bilateral pulmonary tuberculosis.....	1
Polycystic kidney with renal insufficiency.....	1
Advanced Hodgkin's disease.....	1

From this it may be inferred that the diagnosis of renal stone may be of secondary importance in the clinical summary, and that the conditions which may contra-indicate lithotomy are many.

*Stone in the ureter.*—In recent years numerous articles have appeared with reference to the removal of stones in the lower ureter by non-operative methods. Some authors in their enthusiasm claim that it is no longer necessary to operate for ureteral stones since they can all be removed by cystoscopic manipulation. In a previous article I reviewed the methods employed to remove stones in the lower ureter and reported 64 cases in which the stone had been successfully removed. Since then we have been able to bring about the passage of stones in 62 more patients, or in 126 in all. It has been our experience that approximately half of the stones in the lower ureter that will not pass spontaneously can be removed successfully by non-operative measures. This proportion will be greater in larger communities in which the more acute cases with histories of recent symptoms may be observed by the surgeon. In a large number of these early cases

small stones would probably have passed spontaneously even though no cystoscopic manipulation had been made. When the stone has been lodged in the lower ureter during a period of more than from three to six months, and when it is more than 2 cm. in diameter, the possibility of its dislodgment by cystoscopic methods is greatly diminished. In justice to the patient, however, an attempt should be made in every case to dislodge the stone before resorting to operation. It is frequently surprising that by simply dislodging a stone which has been causing symptoms over many months it will be passed by the patient with the next colic. Recent observers have given much importance to the value of drugs which cause the ureter temporarily to relax. It is very questionable, however, what bearing such temporary relaxation could have. Of greater importance is the fact that the stone has been removed from its anchorage by the ureteral catheter, dilating sound or instrument which has come in contact with it. Definite contra-indication to further attempts to dislodge the stone, however, may be: (1) a stone more than 2 cm. in diameter; (2) acute impaction with continuous obstruction; (3) acute renal infection; (4) intolerance on the part of the patient to the cystoscope; and (5) anatomic deformity.

In conclusion I would emphasize the facts that the great majority of renal and ureteral stones will pass spontaneously, that a large proportion of stones in the lower ureter which do not pass after one or two attacks of colic can be dislodged by cystoscopic manipulation, and that immediate operation for small stones, which have caused recent symptoms, is seldom justifiable.

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## STONE IN THE KIDNEY\*

C. H. MAYO

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In medical progress the means of relief by therapeutic measures or surgery have far outstripped our knowledge of the cause of disease. The etiology had been proved in a sufficient number of instances, however, and reasoning by analogy in other diseases had led to measures of prevention and control of many of the common ailments before the identity of the bacterial agents was known. Medicine is in its most interesting phase, namely a consideration of the etiology which carries investigation into the field of biochemistry, the newer physiology, and like sciences. The philosophic view of bacteria is to consider them necessary to life as the minute chemists of the air, the water, and the soil. But few of their countless numbers are the cause of disease by being misplaced in their activity, and only a small number, possibly, are natural disease-creating organisms.

### THE FORMATION OF STONE IN THE KIDNEY

Crystalloids probably form in the structure of the kidney, the cortex and the surface, without local infection, the result of a rare unbalanced contest constantly ensuing between crystalloids and colloids. Stones in the kidney, ureter, or bladder undoubtedly originate in the kidney except those which develop from foreign bodies in the bladder. The cause of stone in the kidney has long been a subject of discussion; the old and simple theory that they grew, like Topsy, is no longer satisfactory, and some of the other theories that have been advanced, although most interesting, are not generally accepted. An acceptable scheme of stone formation must be applicable to the several regions in which stones are found and it must not differ materially for any locality. Morris considers two types of stone, the first due to urinary salts or ingredients precipitated from the urine in the kidney, independ-

\* Presented before the Southern Surgical Association, New Orleans, December, 1919. Reprinted from *Ann. Surg.*, 1920, lxxi, 123-127.

ent of any change in that structure or of infection, and the second, to precipitation due to chemical changes caused by microorganisms. An analysis of stones in the Hunterian Museum has shown a urate nucleus in stones formed in infancy, a uric acid nucleus in stones removed from young adults, and an oxalate nucleus in stones removed from patients in middle life.

Two-thirds of the kidney stones giving trouble are found in patients in the third and fourth decades, although the stones appear in every decade of life. Certain observers hold to the theory that a slowing of the delivery of urine in limited areas leads to increased concentration and deposit of salts. In denying the infection theory they call attention to the fact that renal stones are more often found in men than in women, although the female genito-urinary tract is more likely to be infected. According to their theory, therefore, an increased number of stones should form following mechanical interferences in areas of the pelvis with the passing of urine, such as partial ureteral obstruction and extraneous pressure from glands, tumors, or pregnancy for instance; but this does not appear to be the case. Hunner's theory is not generally accepted, that the over-saturated urine forms stones which originate in the ureter above a stricture of large caliber and may float back into the pelvis of the kidney. It is barely possible that the infection causing stricture may be furnishing mucoid, the cause of stone formation in such a condition. If these hypotheses were true, the number of cases of stone from such causes would be greatly added to by the partial compression of anomalous vessels acting on the ureteropelvic juncture in unusual mobility of the kidney, first shown by W. J. Mayo and later by Rupert to be a very common condition.

Stones are frequently found in both kidneys. Braasch found bilateral lithiasis in 12.3 per cent of 450 cases of nephrolithiasis. Many patients with stone in the kidney have no pain, and 65 per cent with stones in both kidneys have pain on one side only. Cabot by means of repeated tests showed that there are no abnormal urinary findings in 14 per cent of the cases of stones in the kidney and ureter. The kidney is an organ of filtration and is constantly eliminating bacteria from the circulation. These are many in variety and, without some contributing circumstances, apparently do not injure the urinary tract in their passage through the kidney, ureter, and bladder any more than bacteria on the skin or those passing through the alimentary



tract or normally living there cause trouble in those regions. Some types of bacteria produce infarctions in minute clumps of capillaries and following surgical conditions gross kidney infarctions and infection which cause death are occasionally seen. The minute hematogenous infections at the boundary of the terminal circulation in the cortex of the kidney at its juncture with the tubules are seldom extensive enough to create more of a change in the patient's general health than an acne pustule on the face. The eliminating surface of the kidneys probably equals that of the skin covering the body, but the latter has the power of cell growth given to epithelium for restoration as an additional protection. The infection theory seems the only tenable one, but I contend that the development of stone requires the presence of two factors of infection, that is, two types of bacteria, one producing the hematogenous infection, and one only coming from a local focus; the second may but temporarily inhabit the blood in the process of elimination. Bacteria of the stone-forming type must come in contact at the proper time, a brief period only, in which the mucoid exudate is present as a result of the first infection.

It seems hardly possible that the lime content of food or drink, which it must be admitted varies greatly, has very much to do with the origin of stone, although it might influence the rapidity of the growth of the stone. The origin of stone in the kidney is no more mysterious than that of stone on the teeth of infected mouths, which requires a chisel and hammer for removal; saliva resembles the mucoid giving foot-hold through diseased gums for types of bacteria of the proper strain and stone formation ensues; this is true also in the development of gallstones which form only in an infected gallbladder. A step further is the development of the shells of the fresh and salt water mollusks. We think of them as having been built by the mollusk; in reality they are built by bacteria feeding on the pabulum of his exuded mucoid material, according to which the natural type of shell is constructed from the solutions held in the water of the sea or river, the bacteria doing the work for bed and board, the mollusk furnishing the muscle hinge. If these bacteria become misplaced within his body a pearl or slug develops as the result of his disease. Such life can be reproduced only in limited areas of sea or river beds where the bacteria grow in great numbers, producing clam and oyster beds. The work done by such bacteria is no more important than that of the insects which fertilize the fruit flowers.

Stones form in the cortex, in the calices, and in the pelvis of the kidney. The kidney is constantly eliminating living bacteria, so that it is always exposed to infection, and usually shows no results from it except gross lesions of rare occurrence. Stone formation may proceed



FIG. 124.—Infected hydronephrosis with multiple nephrolithiasis.

with exceeding slowness, and without pain or other symptoms until marked destruction of the kidney occurs, mixed infection develops, or until the stone assumes great size or becomes loosened and moves into the ureter (Fig. 124). Minute infarctions occur as shown at necropsy following death from an acute attack, and the results of similar lesions in the past are shown by scars or gross kidney change.

Stone formation is evidently the result of the combination of two types of bacteria; the first creates an infarction with minute necrosis causing mucoid exudate forms; the second factor is the elimination at the same time of the stone-forming bacteria that they may come in contact with the mucoid material. If the stone originates in the cortex of the kidney its growth will be slow, but if it originates in the calices



FIG. 125.—Hydronephrosis with oval stone.

or pelvis growth may be much more rapid because of the ease with which its chemical material is secured.

Stones in the kidney vary in chemical composition but are homogeneous; they are round, irregular, multiple or branched, coral-like (Figs. 125 and 126). Those forming or increasing in the urinary bladder often form rings of varying widths, as shown by cross section. During growth stones are covered with mucus and the changes in structure

probably have to do with the mucoid material on the stone or changes in the metabolic process so that the structure varies with changes in the number of the workmen or the material supplied them. Bacterial types differ in their handling of material as much as masons differ in the use of brick, stone, and cement. It is of interest to note that young oysters transplanted from the shores of England to the Mediterranean

Calices contain pieces broken from large stone



FIG. 126.—Coral-shaped stone with hydronephrosis of the kidney.

oyster beds will have the ray shells formed by the new bacterial architects,<sup>10</sup> a fact of importance in considering branched coral-like stones in the kidney. Medical treatment in principle is based on a change in the chemical conditions of urine or local environment created by food changes, by dilutions, or by elimination of various chemical bacterial detritus. In the review of a limited number of cases in which operation

'19-18

was done during the formative period of surgery of the kidney Cabot found that stone in the kidney reformed in 49 per cent, and stone in the ureter in 29 per cent. Braasch in a consideration of 450 cases of stone in the kidney in which operation was performed showed that the recurrence was slightly under 10 per cent. We believe that this better result is due to more careful examinations made within the last few years, to the greater facilities for all kinds of tests, including roentgenography, especially after operation, in order to discover whether or not a stone has been overlooked; the roentgenogram occasionally shows surprising results in cases of small multiple stones. More careful search must be made for extra stones, since superimposed stones may give but one shadow.

The mortality is low in operations for the removal of stone in the kidney. The reports from the clinic (Table 1) show that the mortality percentage has risen during the past three years over that of the years from Jan. 1, 1898 to Dec. 31, 1915; this is no doubt due to the greater risks which have been taken, but which have resulted in the saving of an increased number of lives.

TABLE 1.—RESULTS OF THE REMOVAL OF STONES FROM THE KIDNEY

	Number of patients	Number of operations	Deaths
Jan. 1, 1898 to Dec. 31, 1915	450	484	3 (0.62 per cent)
Jan. 1, 1916 to Dec. 1, 1919	487	499	8 (1.87 per cent)
	937	983	11 (1.12 per cent)

In closing I wish to call attention to a plan devised by Dr. Braasch and Dr. Carman of the clinic to prevent overlooking stones in the kidney at operation and to facilitate search for small stones giving symptoms that are difficult to locate in the pelvis, the calyx, or the cortex of the kidney. In the course of the operation the kidney is elevated into the incision, above the level of the skin if possible, where it is held by an encircling pack of gauze; a portable x-ray apparatus of the army type is moved to the side of the operating table and under the darkened glass and hood the roentgenologist is at once enabled to locate the stone and to point out the location with an aseptic glass rod, or, what is just as important, and occasionally occurs, he proves that the shadow seen in the roentgenogram was not due to stone in the kidney, and thus prevents serious injury to the organ by a fruitless search. The roentgenologist wears darkened glasses for fifteen minutes before attempting

such an inspection. The operating room is darkened and the operator works under electric light which can be turned off and on.

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## THE RESULTS OF OPERATIONS FOR THE REMOVAL OF STONES FROM THE URETER \*

E. S. JUDD

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Within the past few years many ingenious non-surgical methods for the removal of stones from the ureter have been devised and described, thus greatly reducing the need for operation in these cases. It is first to be desired in cases of stone in the ureter that the stone shall pass voluntarily into the bladder. In some instances this will occur during the first attack of pain although usually several attacks are required to force the calculus through. Without special investigation of this subject it may not be realized how many persons pass stones spontaneously. I have known of 12 per cent of a group of about 400 persons to respond in the affirmative when they were questioned with regard to the passing of stones.

The published data and our own experience seem to show that most of these calculi originate in the calices and in the kidney pelvis. In some of the cases in which there is an associated stricture of the ureter the stone may originate at the point of the stricture, as suggested by Rovsing and Hunner; in most of our cases, however, in which a definite firm stricture was found there was no evidence of a calculus.

The symptoms produced by ureteral calculi are usually very definite and suggest the condition even though in a number of cases the stone may lie in the ureter for a long time without any apparent changes or symptoms. In several such cases we have not seen changes of any consequence in the ureter or the kidney, nor evidence of interference with the passage of urine. In by far the larger number of cases the characteristic symptoms are manifest, but the syndrome must not be depended on for the diagnosis since it may be misleading; a variety of other conditions may produce nearly the same syndrome and, furthermore, an accurate and dependable diagnosis can be made in nearly every case by the use of the x-ray combined with the opaque

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catheter and ureterogram, and in some cases the wax-tip catheter. In doubtful cases in which it is necessary to exclude the possibility of the x-ray shadow which is being produced by an extra-ureteral structure, Dr. Braasch employs ureterograms, and by this method has reduced the possibility of error to an inconsiderable degree.

When the diagnosis has been made and the exact location of the stone is determined there are several points to be considered regarding the plan to follow. We must first remember that in many cases the stones will pass of their own accord so that if the patient is having frequent and severe attacks of pain it will probably be best to keep him under observation for a reasonable length of time in the hope that the stone may pass unassisted. During this waiting period, however, the possibility of too severe pressure in the ureter and kidney and of a permanent hydronephrosis or pyelonephrosis should constantly be kept in mind in order that this waiting time shall not be too prolonged. In cases in which the stone apparently is not causing symptoms, even when it is discovered in the course of a routine examination, its removal is advisable unless there is some contra-indication. In all the cases in which the stone does not pass readily of its own accord it is best to consider the non-operative methods of treatment.

Patients with stone in the ureter who come to the clinic for treatment are seen and examined in the Section of Urology. After the diagnosis has been made the non-operative methods are employed. Braasch,<sup>2</sup> who has removed about 126 calculi in this manner, dislodges the impacted calculus by a ureteral catheter or a small sound. His results have been very satisfactory, and he believes that all patients should have the benefit of an attempt to remove the stones without operation. Braasch's definite contra-indications to further attempts to dislodge stones are: (1) a stone 2 cm. or more in diameter, (2) acute ossification with continuous obstruction, (3) acute renal infection, (4) the patient's intolerance to cystoscopic manipulation, and (5) anatomic deformity. If the renal infection is severe intra-ureteral methods should not be attempted, and the operation should be undertaken with the idea that it may be necessary to remove the kidney.

The results of non-operative methods to give the best results will depend largely on the manner in which they are used. Braasch has obtained excellent results by dislodging stones with ureteral catheters and he has also had some good results with papaverin. In nearly all the cases in which the stone presents at the ureteral orifice he has



succeeded in removing it by means of the Bransford Lewis and other types of instruments. It is difficult to decide just how many times these non-operative measures should be repeated; the success of the attempt and the pain and discomfort to the patient may well be deciding factors. In some cases, undoubtedly, such treatments have been carried too far, producing infection in a normal kidney, and considerable trauma to the ureter and bladder. It should be borne in mind that while this non-operative treatment was being perfected many improvements were made in the surgical treatment, and the results of operative procedures are now very satisfactory.

A stone lodged in the ureter may result in pathologic changes in several different tissues. In many cases the ureter is dilated above the stone and in some instances this dilatation is marked, so that the ureter seems almost as large as the small intestine. In such cases the wall of the ureter is thick, with definite signs of inflammation. At times the stone completely blocks the ureter and there is an accompanying hydronephrosis. Unless the kidney is extensively infected it need not necessarily be removed, since after the stone is removed sufficient renal function may remain to warrant saving the kidney. The same condition may result whether the stone is large or small. Contrary to this is the case in which the ureter, on exposure, appears normal in size and appearance, a condition noted in many of our cases. The stone seems almost to fill the lumen of the ureter and yet there is no dilatation and no evidence to show that the ureter has previously been dilated. The improbability that these stones descend through the apparently normal ureters seems to be evidence of the fact that some of these calculi may form in the ureter itself, possibly at the site of a stricture. This type of stone is small and is often located with difficulty in a seemingly normal ureter. It is undoubtedly true that stricture of the ureter occurs in association with stone, and it is quite probable that in some of our cases in which there was not immediate complete relief of symptoms after the stone was removed that a stricture caused the trouble. I have been impressed with the infrequency of any gross evidence of a stricture. Even in cases in which difficulty was experienced in removing an inaccessible stone and in those in which the stone had perforated the ureter and produced much peri-ureteral infection we have not seen a stricture of any consequence. In some of our cases there was delay in the closure of the urinary sinus, but in all the sinus was completely closed within a few weeks, and no

permanent fistulas occurred. There must have been stricture in some of our cases, but I believe that in most instances the condition is spontaneously relieved.

The same conditions follow the removal of stone by the non-operative and the operative methods. In several cases we have found the ureteral calculus lying in an abscess cavity outside the ureter, and in all of these the condition was relieved by the removal of the stone from the abscess pocket and drainage of the abscess without any endeavor to manipulate the ureter. If a pyelonephritis has resulted from the stone and there is no evidence of more or less general infection it is advisable, if there is a good functioning kidney on the opposite side, to remove the stone and establish drainage. In many of these cases the damage to the kidney is already beyond recovery, the immediate results will not be satisfactory, and the kidney will have to be removed later. In the extreme case, if the stone is in the lower third of the ureter so that a very large incision, or in some instances two incisions, would be required to remove the kidney and the ureteral stone, it is best to remove the kidney and leave the ureter and stone, removing the stone later if necessary. In two of our cases we were obliged to remove the calculus from the ureter at a later date because of pain. Before operation it may be impossible to determine the amount of function in the affected side as it is sometimes impossible to collect the urine because of the presence of the stone. In these cases I believe the best plan is to remove the stone and preserve the kidney if we are not aware of infection in the kidney at the time. Conservative methods are justified in any case of chronic infection of the kidney, but radical methods must be employed in acute severe infection, and nephrectomy should be done before severe uremia and toxemia threaten.

In two of our cases complete anuria was produced by stone in the ureter. In Case 1 (A195194), the patient had been operated on by Dr. W. J. Mayo five weeks before for hypernephroma of the left kidney. The patient made an uneventful recovery from the nephrectomy, was discharged from the hospital, and was about to leave for home when he noticed that his urine had diminished greatly. He told of having passed stones, probably from the right side, some time before and of having colic, which suggested a stone on the right side. Finally the urine stopped completely and treatment was instituted for suppression, but aside from the fact that there was a little evidence of edema the patient did not appear to be sick. Dr. Crenshaw cath-

eterized the right ureter and met an obstruction about 5 inches from the bladder which the x-ray showed to be a stone. The patient had passed no urine for six days when I operated, removing the stone from his right ureter. The ureter was greatly dilated and filled with turbid urine. The kidney started to functionate apparently as soon as the pressure was relieved, a large amount of urine was secreted, and the patient made a complete recovery.

In Case 2 (A205789) the man gave a history of having been operated on several months before for stone in the left ureter. He came to the clinic because of a persistent urinary sinus through the scar on the left side. Dr. Braasch's examination revealed a stone in the right ureter about 6 inches from the bladder, and a ureteral catheter was passed to the scar of the operation on the left ureter. The patient was passing about equal amounts of urine from the bladder and the sinus in the left flank. Shortly after the examination the urine stopped completely. We tried again to probe the urinary sinus on the left side but were not successful. For six days there was no urine passing from the sinus or the bladder and yet the patient apparently was having no trouble because of it. I then removed a stone from the right ureter which was greatly dilated and filled with turbid urine as in Case 1. Because of the evident infection no effort was made to close the opening in the ureter and the urine drained for several days, after which the wound healed completely. At this time the sinus on the left side, which we had not been able to open with a probe, opened spontaneously and drained urine. A month after removing the stone from the right side, I operated through the scar on the left side, and closed the left ureter which was greatly scarred and thickened. Examination of the ureter revealed no cause for the persistent sinus and trouble except extension of scar tissue and stricturing. I excised much of the scar tissue and reconstructed the ureter over a small tube, which was pushed down the ureter so that it projected into the bladder. The tube was removed some days later by means of the cystoscope. The sinus did not reform and the ureter was patent at the time the patient was discharged.

The most striking feature in both these cases is that, in spite of the fact that no urine escaped for six days, the patients did not appear to be sick.

In our few cases of bilateral ureteral calculi, it has seemed best to remove the stones by operation rather than by non-operative

methods. We usually operate on one side at a time, although in some instances we have removed stones from both ureters at one operation. The side showing evidence of acute trouble is operated on first; if there is no apparent difference we prefer to remove the stone from the ureter on the side having the best function.

The cases in which operation has been done between the years 1901 and 1918 are tabulated in Tables 1 to 14. During this same time, Dr. Braasch has removed ureteral stones in 126 cases by non-operative methods. During the same period we operated on 400 patients. In our earlier cases no attempt was made to remove the stone by non-operative methods. We find it is difficult to estimate just what percentage of ureteral calculi may be removed by non-operative methods, but probably the percentage is often given too high. Roughly estimated, I should say that at the present time about one-half the patients require operation in order to rid them of the stone; in other words, they will be better off if the stone is removed by operation.

Forty-eight (12 per cent) of the 400 patients operated on had passed stones or gravel before operation; in 9 cases multiple stones, averaging 6, had been passed, and yet in all these cases impaction of a stone in the ureter necessitated operation.

The diagnosis of ureteral stone by x-ray and cystoscopy has been developed almost altogether since 1901, so that a much higher percentage of accuracy in diagnosis will be found in the later cases than in the cases of earlier years.

Our study shows that the results of operations for the removal of stone in the ureter have been almost universally satisfactory. Of this series of 400, two of the patients operated on have died and only one of these deaths could be attributed to the operation. In the first case an infected appendix was removed; the patient had a left hydro-nephrosis and a right-sided nephritis; he died of peritonitis. In the second case death resulted at about the end of two weeks from infection and extravasation of urine.

Convalescence following the operation is usually short and not attended by any difficulties. In some instances the urine drains freely for several days, and in others, even though the opening in the ureter has not been closed, there will be very little if any drainage. In the non-infected cases in which it is feasible to close the opening in the ureter, the wound heals primarily.

During the past few months, Dr. Scholl has made a careful review of the histories of these cases, and has sent out "follow-up" letters to all the 400 patients; answers have been received from nearly 300. In approximately 90 per cent of these complete relief of former symptoms had ultimately resulted. A number of the patients mentioned the fact that they had pain in the same side and of the same character persisting for several weeks after the operation, but in most instances by the end of six months the pain had entirely disappeared. Twenty-one patients had pain severe enough at some time or other to require

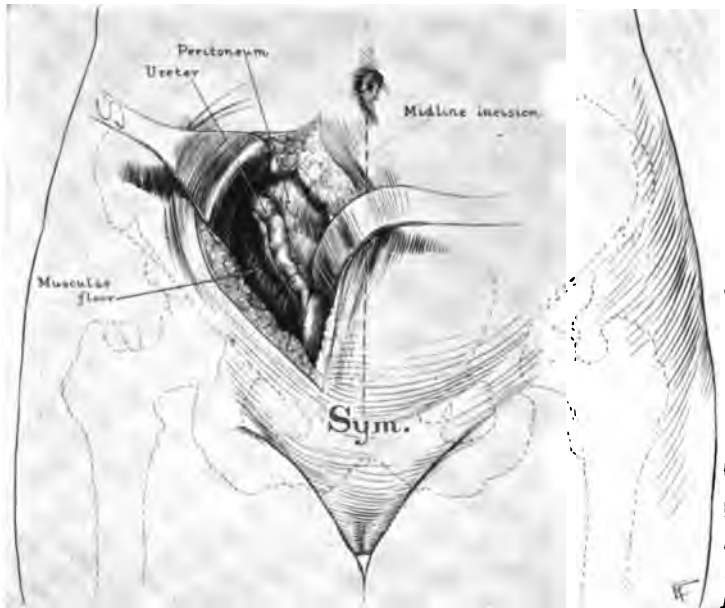


FIG. 127.—The midline incision is used when it is necessary to explore both ureters.

morphia. About 15 per cent of the patients complained of frequency, and some of them of hematuria lasting for several weeks after the operation, thus showing that the infection which existed at the time of operation had a tendency to clear up later. Twenty-six of the 400 patients have passed stones since the operation. Of course it is impossible to say whether these stones came from the kidney, the ureter on the side operated on, or the opposite side.

The technic of the operation for the removal of stone from the ureter differs according to the location of the stone. If the stone is

situated at the uretero-pelvic juncture, or at any place in the upper third of the ureter, the best approach is through the Mayo posterior-lateral incision, the same incision as employed to explore the kidney.

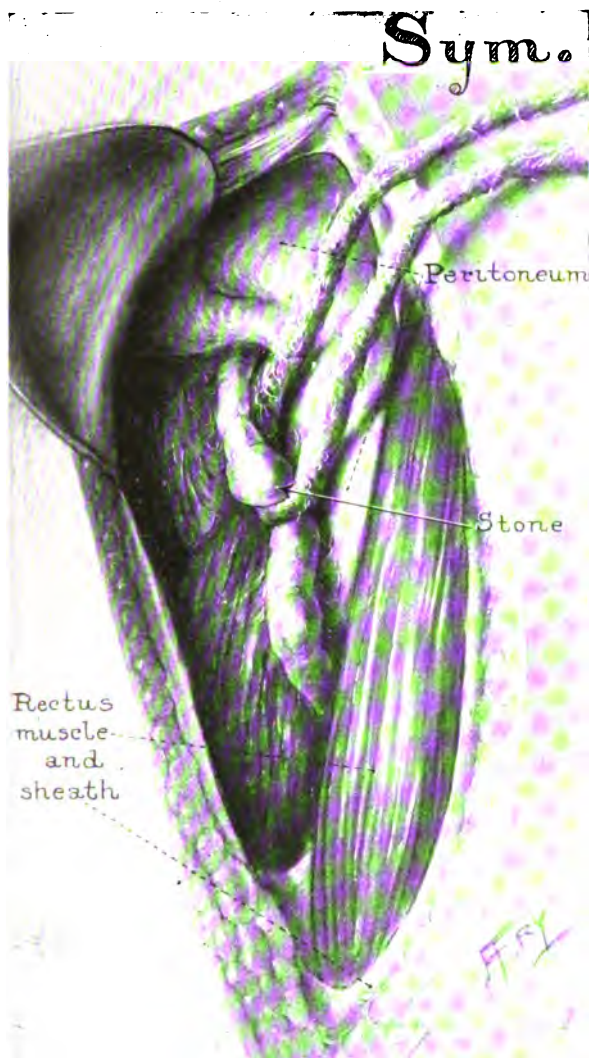


FIG. 128.—Isolated ureter containing a stone.

If the calculus is situated in the lower two-thirds of the ureter, the straight rectus incision gives the best exposure (Fig. 127), the exact



FIG. 129.—Incision in ureter showing a stone.

position of the incision depending on whether or not the calculus is in the middle or lower third of the ureter. Under ordinary circumstances the operation should be performed without opening the peritoneum since less opportunity is allowed for infection. If the peritoneum is accidentally opened it should cause no alarm although care should be taken accurately to close it. Since the retroperitoneal space is opened by retracting the peritoneum away from the posterior muscles the ureter will probably retract with the flap of peritoneum so that the search for the ureter should be made on the posterior surface of the peritoneum and not on the anterior surface of the muscle. If the stone



FIG. 130.—Interrupted catgut sutures being placed to close incision in ureter. Sutures do not pass through mucosa.

is large the ureter is usually readily located by palpation. The greatest difficulty arises in locating a small stone in the lower end of a non-dilated ureter; fortunately this is the type of case most often relieved by conservative methods. Several years ago I called attention to a technic for exposing this part of the ureter and removing such stones.<sup>4</sup> The operation consists in complete exposure of the lower end of the ureter in the manner employed in operating on the bladder for neoplasm or diverticulum. The entire lower third of the ureter is brought into view (Figs. 128 and 129). After the stone has been removed it is best, I believe, loosely to close the opening in the ureter. Since Abell



reported the series of cases in which he employed this technic I have used it many times without any ill-effects and, I am sure, that it has made convalescence much easier and shorter. The ureter has not healed in all cases without some drainage, but it has in many, and in others the urinary drainage was very slight. Stitching the ureter without penetrating the mucosa seems to be of distinct advantage.

TABLE 1.—PATIENTS WITH URETERAL STONES OPERATED ON AT THE MAYO CLINIC  
1901-1918 INCLUSIVE

Total number.....	400
Males.....	248
Females.....	152
Location:	
Right ureter.....	197
Left ureter.....	195
Bilateral involvement.....	5
Not stated.....	8

TABLE 2.—AGE AT ONSET OF SYMPTOMS

	Cases
0-10 years.....	10
10-20 years.....	38
20-30 years.....	129
30-40 years.....	125
40-50 years.....	61
50-60 years.....	25
60-70 years.....	8
Average age.....	32.4 years

TABLE 3.—AGE OF PATIENTS ON ENTRY TO HOSPITAL

	Cases
0-10 years.....	4
10-20 years.....	5
20-30 years.....	87
30-40 years.....	135
40-50 years.....	108
50-60 years.....	42
60-70 years.....	12
70-80 years.....	2
Average age.....	37 7 years

TABLE 4.—DURATION OF SYMPTOMS

	Cases
1 year.....	138
2 years.....	60
3 years.....	27
4 years.....	23
5 years.....	22
5-10 years.....	62
10-15 years.....	33
15-20 years.....	19
20-30 years.....	11
Average duration of symptoms.....	4.8 years
Patients entering hospital after symptoms of 1 year's duration.....	34 per cent
Patients entering hospital after symptoms of 2 years' duration.....	49 per cent

TABLE 5.—PAIN REFERRED TO

	Cases
Region of kidney.....	281
Right loin.....	123
Left loin.....	142
Both sides.....	16
Lower abdomen.....	55
Right.....	33
Left.....	22
Suprapubic region.....	5
Upper abdomen.....	63
Right.....	34
Left.....	27
Epigastric region.....	2
Genitals.....	5

TABLE 6.—BILATERAL KIDNEY PAIN

	Cases
Stone in opposite ureter also.....	4
Stone in opposite kidney also.....	5
Pyelonephritis on opposite side.....	1
Not determined.....	6

## GROSS HEMATURIA

71 cases..... 17.4 per cent

## BLADDER IRRITABILITY

129 cases..... 32.1 per cent

## CONCLUSIONS

1. The study of this series of 400 patients operated on for ureteral stone and the 126 patients treated by Braasch, leads us to conclude

that before instituting any method of treatment for the removal of stones from the ureter, it is well to bear in mind that a large percentage of such stones pass voluntarily; in the early cases, therefore, it is best to delay treatment.

2. Unless there are definite contra-indications to non-operative treatment for the removal of the stones, an attempt should be made to remove them by non-operative methods. We doubt the advisability of attempting to remove stones from the middle and upper third of the ureter in this manner, but believe that with the development of the method nearly all small stones may be removed from the lower end of the ureter without operation.

TABLE 7.—URINALYSIS

	Cases
Pus.....	102
Blood.....	39
Pus and blood.....	191
	<hr/> 332 (82.6 per cent)

TABLE 8.—X-RAY FINDINGS

	Cases
Positive.....	295 (60 per cent)
Negative.....	36 ( 9.0 per cent)
Negative in 1919.....	11 ( 5.7 per cent of 193)

## CYSTOSCOPIC FINDINGS

Definite obstruction to ureteral catheter.....	240 (60 per cent)
No obstruction.....	109 (27.2 per cent)
Stone visible at meatus.....	1 ( 1 per cent)

TABLE 9.—PREVIOUS OPERATIONS

	Cases
Ureteral stone, same side.....	3
Ureteral stone, opposite side.....	1
Renal stone, same side.....	4
Renal stone, opposite side.....	1
Negative renal exploration, same side.....	3
Negative renal exploration, opposite side.....	1
Nephrectomy, opposite side.....	5
Nephrectomy, same side.....	2
(Nephrectomy was done five and seven years before, but stone was left in the ureteral stump.)	
Bladder stone.....	2
Appendectomy.....	54
Other abdominal operations.....	68
	<hr/> 144

3. While the operation for the removal of calculi from the ureter must be considered a major operation, it may be performed with practically no mortality and with universally good results. Therefore, if there is a definite contraindication to non-operative treatment or if progress is not being made by such treatment, the stone should be removed by open operation without hesitation.

TABLE 10.—NEGATIVE EXPLORATIONS

	Cases
Stone found in bladder.....	5
Definite signs of stone found at operation (stone had probably passed before operation).....	3
Stone passed one month after operation with definite renal colic (stone probably in ureter but not located).....	1
Probable mistaken diagnosis.....	4
Mistaken diagnosis in 1919 group of 193 cases.....	1

TABLE 11.—LOCATION OF STONES

	Cases
Ureteropelvic juncture.....	38
Upper third of ureter.....	49
Middle third of ureter.....	7
Iliac crest.....	4
Lower third of ureter.....	198
Ureterovesical juncture.....	53
Intramural.....	32

TABLE 12.—BILATERAL INVOLVEMENT

	Cases
Bilateral ureteral.....	5
Stone in same kidney.....	29
Stone in opposite kidney.....	9
Stone in bladder.....	1

TABLE 13.—DURATION OF SYMPTOMS BEFORE NEPHRECTOMY FOR URETERAL STONE

	Cases
1- 5 years.....	22
5-10 years.....	11
10-15 years.....	8
15-20 years.....	6
20-25 years.....	2
25-30 years.....	2
Average.....	8.5 years
(16 of these patients had stone in the kidney also.)	

## MORTALITY

Case 216040: Operation, ureterolithotomy; patient died thirteen days after operation; marked urinary extravasation was found.

'19-19

Case 72640: Operation, combined ureterolithotomy and appendectomy; patient died of general peritonitis.

TABLE 14.—INFORMATION RECEIVED IN ANSWER TO "FOLLOW-UP" LETTERS

Operations since leaving the clinic.....	12
For ureteral stone, opposite side.....	2
For ureteral stone, same side.....	0
For renal stone, opposite side.....	1
For renal stone, same side.....	1
Nephrectomy, same side.....	4
(1 case complicated with nephrolithiasis)	
Nephrectomy, opposite side.....	1
Negative renal exploration, same side.....	3
Stones passed since operation.....	31
Stones passed previous to operation.....	48 (12.3 per cent)
Multiple stones (averaging 6) passed previous to operation.....	9

Letters received on an average of four and one-half years after operation stated that ureteral stone had occurred on the same side in 3 cases, in 2 the first operation had been performed in the Mayo Clinic, and in one it had been performed elsewhere.

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## SURGERY OF THE URINARY BLADDER\*

E. S. JUDD

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The bladder, situated beneath the pubic bones, is not so accessible for surgical intervention as the other abdominal viscera. Instead of being covered by a layer of protective peritoneum it is almost completely encased in a fatty tissue which offers little if any resistance to infection. The inaccessibility of the organ and the difficulty in preventing infection are the sources of trouble in surgery of this region. However, the functional results obtained even after extensive operations are very gratifying.

It is possible to remove a large segment of the wall and still maintain practically normal functional conditions. Urine enters the bladder by spurts and jets under the influence of a small sphincter muscle at the ureterovesical juncture, although this tiny muscle may be sacrificed in one or both meatuses without serious consequences;<sup>3</sup> the only difference is that the urine enters the bladder in a continuous stream. In a large series of cases lesions requiring surgical intervention at or near one of the ureteral orifices have made it necessary to sever the ureter and reimplant it into another segment of the bladder. By follow-up letters to patients it has been found that the kidney was functioning normally years afterward without infection or hydronephrosis.

Our experience is now sufficient to enable us to assert that while severing and reimplanting the ureter offers some additional risk, it is not sufficient to contra-indicate the procedure if by it a better ultimate result can be obtained, as in cases in which malignancy is suspected. If transplantation makes recurrence less likely, it certainly should be done. Severing and transplanting both ureters at the same time offers only the additional mechanical difficulty of implanting the

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Reprinted from *Journal-Lancet*, 1920, xl, 6-9.

ends of the ureters free enough to insure their remaining open during the period of healing, with the consequent swelling and edema. We have successfully reimplanted both ureters in several instances.

In certain cases the end of the ureter may be involved in the malignant process so that when the disease is thoroughly removed the ureter is not of sufficient length satisfactorily to be implanted in the bladder. In such cases we now ligate the ureter and allow it to drop back into the wound. This procedure was adopted with much trepidation. Our first case was that of a patient on whom a great deal of operating had just been done and either nephrectomy or intestinal transplantation was out of the question. We thought that it would be necessary to remove the kidney within a few days; however, it was not necessary, nor has it been in subsequent cases. The ligation of the ureter has not appeared to add greatly to the seriousness of the situation. We do not hesitate, therefore, to ligate the ureter whenever the necessity arises and when we are sure that the opposite kidney is in good condition and is functioning.

In resections of the bladder for a lesion at and obstructing the end of the ureter with a hydroureter I believe it is probably as safe to ligate the ureter as to implant it. Just what occurs in the parenchyma and pelvis of the kidney when the ureter is ligated has not been definitely determined and cannot be worked out satisfactorily by animal experimentation. We have ligated the ureter many times during the course of operations and we have not found a resulting hydronephrosis although we have followed some of these cases for a long time, while in all the animals on which the operation has been done a hydronephrosis occurred.

Weld has recently endeavored to determine the results of ligating the ureter in animals. He filled the kidney pelvis with a solution which shut out the x-rays as soon as the ureter was ligated; then frequent exposures of the kidney were made extending over a considerable period of time. He thought that by watching the outline of the kidney pelvis he could discover any tendency toward hydronephrosis. After the ureter had been ligated and the pelvis distended in this manner, however, no change in the shape of the pelvis could be demonstrated, but the salt solutions introduced into the kidney pelvis under these conditions were very quickly absorbed. For instance, phenol-sulphonephthalein left in the pelvis after ligation of the ureter appeared in the urine from the other kidney in a very few minutes. Such find-

ings should be of great importance in convincing us of how readily infection, which gets into the kidney pelvis, may be generally distributed. Undoubtedly when the ureter in man is ligated the back pressure from the secreted urine is equal to or greater than the blood pressure in the kidney so that the blood is very soon shut out of the kidney and it ceases to functionate and becomes practically scar tissue. Ligation of the ureter in a dog is apparently always followed by a hydronephrosis, and this may increase in size, rupture, and cause death. It was at first assumed that this difference might be caused by the kidneys receiving a blood supply through the capsule after the renal vessels had been compressed. In order further to study this condition in several experiments we ligated the ureter and stripped the capsule from the kidney and it seemed to us that the same degree of hydronephrosis developed in the kidneys from which the capsule had been removed as in those from which it was not removed after ligation of the ureter.

It has recently been established in experimental work on animals and it has practically been established in man (Caulk and Fisher), that the ureter may be occluded for a number of days (the longest time about fourteen days); if the lumen of the ureter is re-established the kidney will gradually begin to functionate and will usually return to its normal function. We have had a similar experience although the conditions differ slightly. The ureter had been completely blocked for at least six days by a stone, and the kidney functionated within a few days after removal of the stone. The fact that the kidney will survive and re-establish its function even after the ureter has been occluded for some time, should be remembered in connection with the traumatization of the ureters which occasionally occurs in extensive pelvic operations.

At least one half the bladder may be removed and good function obtained. It has been suggested that these small bladders gradually increase in size until they are normal; if a very large segment is removed, however, it is probable that the size will remain diminished as is evidenced by frequency of urination.

The most important consideration in surgery of the bladder is the preservation of the sphincter muscle at the urethral orifice. This is necessary if the patient is to maintain any degree of comfort. If the question arises of whether or not the sphincter is to be sacrificed it is best to view the condition as inoperable for the patient will practically



never be satisfied without urinary control. The only alternative is to reimplant the ureters into the intestinal tract, a satisfactory procedure in many cases as the rectal sphincter will control the urine.

In operating for the unfortunate condition known as bladder exstrophy it has been our plan for a number of years to reduce the prolapsing bladder to the abdomen by some plastic measure and to maintain it there by closing over the wall. These operations have been successful mechanically, but they are not satisfactory from the patient's standpoint as he has no better control of urine than before. In these cases also since there is no sphincteric control it is best to transfer the ureters to the colon, depending on the rectal sphincter to control the urine. C. H. Mayo has shown that this control is very often satisfactory. The objection to it is the possibility of infection ascending from the intestinal tract by way of the ureter to the kidney, which has undoubtedly occurred in many cases. However, with the technic of implantation of the ureter suggested by Coffey and by Stiles, the likelihood of severe ascending infection has been greatly reduced. The operation is a serious procedure, but it improves the condition more than any other.

Another extremely interesting anomaly is the extravesical opening of the ureter. The ureter may open into the vagina or into the uterus. It may be the only ureter on that side or the two ureters may be present in their normal positions with an additional ureter on one side opening extravesically. In these cases the history usually shows that there has always been more or less urinary incontinence. Sometimes, apparently, the ureter closes for a time, then opens and drains again. In our experience, this condition has been found more frequently in girls and is recognized by the fact that in addition to the normal urination there is a persistent incontinence. It is often difficult to locate the extravesical opening. The condition is rare and may easily be overlooked or thought to be sphincter incontinence, a condition which practically never occurs in young women.

Diverticulum of the bladder undoubtedly is very often congenital. The condition is being recognized much more frequently than formerly and is probably the cause of many cases of protracted cystitis, especially those associated with obstruction caused by the prostate. Diverticula are very satisfactorily treated surgically.

Foreign bodies are frequently found in the bladder.<sup>5</sup> It is of in-

terest to note that a foreign body, such as a piece of bone from an osteomyelitis, or a piece of metal which had been thrust into the soft tissues above the buttocks, may gradually work its way into the bladder without producing symptoms of urinary soiling in the tissues.

The etiology of the formation of bladder stones and the frequency of their recurrence in certain persons is undoubtedly due to some type of infection. The risk of removing stones in old persons is not due to the operation itself, but to poor resistance and the existing infection; with a stone in the bladder, the kidney function is likely to be reduced.

Rupture of the bladder is a frequent occurrence, but if the condition is recognized and treated early, all the patients get well. Often the rupture extends into the peritoneal cavity and it is necessary to sponge out the urine. This type of peritonitis, however, is rarely fatal. Operation is indicated in any case of bladder rupture, no matter how late it is recognized.

A very unfortunate injury is that of fracture of the pelvis and the tearing away of the neck of the bladder and the urethra. I have not had a great deal of experience with such cases at the time of the injury, but I believe that more attention should be paid to establishing some sort of a urethra immediately. If scar tissue is allowed to form after the injury, it is almost impossible later to develop any kind of urethra. We see many patients in this condition each year, and while the urethra may be forcibly dilated a satisfactory result is seldom obtained even after several years of treatment. In instances in which I have seen the patient early, I have been able to penetrate the traumatized tissue and establish a urethra at once.

Inflammation of the bladder alone is not common, but inflammation in the bladder in conjunction with the same process in the kidney or other parts of the tract is common.

Tuberculosis never occurs in the bladder alone although it is present in most cases of tuberculosis of the kidney. Cystitis, which was formerly considered common is now an unusual occurrence except as a part of an infection in some other part of the genito-urinary tract. The same general statement may be made concerning ulcerations in the bladder. The submucous ulcer, a condition described by Hunner, is being widely discussed. It may occur as a very small lesion in the mucosa and then become an extensive edema in the submucosa and muscularis. There are no urinary changes. The symptoms are ex-

treme irritability and frequency. It is difficult to recognize the condition as the findings are slight. The differential diagnosis lies between a submucous ulcer and the bladder symptoms of a neurasthenic.

The surgery of vesical neoplasms<sup>6</sup> has not been altogether satisfactory. Fulguration undoubtedly has helped in the treatment of small papillomas, but, on the other hand, it has not always been judiciously used and many patients who might have been operated on satisfactorily have lost that chance by continued fulguration which was of no benefit.

Cancers of the bladder should not be fulgurated, and in any type of case in which fulguration does not promptly relieve operation should be done. Operation is of great benefit in cases of early malignancy of the bladder, but there is not much to be derived from extensive operation after the growth has penetrated the wall of the bladder.

In operating for tumors of the bladder it is necessary to make a large incision in order to obtain sufficient exposure and to remove the prevesical tissues widely with the bladder wall. The transperitoneal operation is necessary only in those cases in which the growth is on or close to that portion of the bladder.

Operations on the bladder, especially for bladder tumors, must be done in the same manner in which the operations for neoplasms of the stomach and intestines are done. The principles of general surgery must be employed in this field, with the same surgical judgment and technic, if the good results secured elsewhere are to be obtained here.

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## SECONDARY MELANO-EPITHELIOMA OF THE BLADDER\*

C. G. RICHARDS

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Melano-epithelioma is always primary in the eye or in pigmented moles of the skin, and it metastasizes so rapidly that the patient succumbs soon after the appearance of the growth. The extreme rarity of its occurrence in the bladder seems to warrant the report of the clinical history and subsequent course of the disease in a case under our observation. Mention has been found in the literature of but one similar case.<sup>1</sup> The history of our patient is as follows:

CASE 218587.—A man, aged 45, stated that his mother had died of cancer of the stomach at the age of 73, and, like himself, had had pigmented moles irregularly distributed over the entire body. For the past five or six years the patient had noticed that a rather large mole situated on the right side of the abdomen near the umbilicus had a core of granular debris which could be expressed, and two months previous it had begun to enlarge and had a tendency to bleed. Because of the bleeding the patient consulted his physician who excised the growth. Histologic examination revealed melano-epithelioma. Further surgical advice was sought. The examination was negative except for slight enlargement of the inguinal lymph nodes. The urinary findings were negative. A gland removed from the groin was found to be malignant and therefore all the lymphatic glands in both groins and Scarpa's triangle were removed; the external saphenous vein was ligated. While the patient was convalescing from the operation radium treatment was begun, and was continued at frequent intervals. Eight months later another small gland in the inguinal region was discovered, which proved to be of the nature of those previously removed. Ten months later increased frequency of urination and diminution in the size of the stream, and nocturia

\* Reprinted from Surg. Gynec. and Obst., 1919, xxix, 266.

were noticed. The urine contained a number of erythrocytes and pus-cells.

On cystoscopic examination multiple areas of black rounded tumors varying in size from 2 to 5 cm. were found on the right base of the bladder anterior to the right meatus. On the left wall two of the tumors had pedicles; the other were sessile.

As soon as the bladder condition was discovered the intravesical radium treatment was instituted. To the present time 400 mg. hours have been given. At the last cystoscopic examination one month ago no material change was noticeable except perhaps a slight increase in the size of one or two of the tumors.

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## DIVERTICULA OF THE POSTERIOR URETHRA\*

H. C. BUMPUS

The repeated finding of diverticula of the posterior urethra during routine cystoscopic examination led to a search through our records and the literature for similar cases. As was expected, few were found.

The literature, as reviewed by Ehrlich, revealed but 70 cases of urethral diverticula up to 1908. Watts reported one case and reviewed the literature in 1906, and Englander added 2 cases in 1917. In our cases the diverticula were all confined to the posterior urethra; their clinical histories vary considerably from those reported in the literature.

Watts, besides his complete and thorough review of the literature, gave an excellent classification of urethral diverticula which we have adopted:

A. Congenital diverticula.

B. Acquired diverticula.

1. From dilatation of urethra due to

a. Calculus.

b. Stricture.

2. With perforation of urethra resulting from

a. Injuries to the urethra.

b. Rupture of abscesses into the urethra.

c. Rupture of cysts into the urethra.

A differentiation is also made between true and false diverticula. The former is a dilatation of the normal urethra with a mucous membrane lining identical with that part of the urethra from which it arises. The latter is the result of urethral rupture and, therefore, has a lining of epithelium or fibrous tissue according to the extent of repair that has occurred. Of the true diverticula the congenital offers the most perfect type. It occurs in the anterior urethra and is probably the result of a failure of the urethral floor to close during fetal life, a con-

\* Reprinted from Surg. Gynec. and Obst., 1919, xxix, 388-392.

dition similar to that of hypospadias, or, as Watts suggests, a condition due to congenital stricture or phimosis.

Diverticula of the posterior urethra are probably always of the acquired type and usually traumatic in origin. Surgical procedures about the perineum either for the drainage of the seminal vesicles, as in Case 1, or for the removal of the bladder or prostatic stones, as in Case 4, are probably the most frequent factor in their formation. Frequently the falling astride some hard object with resulting rupture of the urethra or the formation of a hematoma with secondary rupture into the urethra results in their formation. Strictures are also an etiologic factor, both because of their tendency to cause dilatation posteriorly and because of the inaccurate passage of sounds in an attempt to dilate with resulting false passage and urethral rupture. Abscess formations in the neighborhood of the posterior urethra or in the seminal vesicles, as in Case 3, with secondary rupture and drainage into the urethra are frequently the origin of diverticula.

In cases in the literature a tumor at some point along the urethra is an almost constant finding, and the history of being able, by digital pressure, to express varying amounts of urine from such a mass is considered very suggestive. In our series but one patient (Case 4) gave such a history. This fact seems most pertinent, as our illustrations show to what size such diverticula may develop and yet give no physical signs; they even burrow under the bladder until they nearly equal it in capacity (Fig. 135). Lane reported several cases similar in character, found at necropsy, and Isaacs reported one that caused death by rupturing into the peritoneal cavity with resulting peritonitis.

Diverticula of the posterior urethra give a series of symptoms which are the result of a chronic inflammatory process going on in close proximity to the sphincter musculature and involving the urethra itself: (1) Dribbling or complete incontinence, depending on how near the diverticulum is to the external sphincter, and to the extent it has become involved in the inflammatory tissue produced by it; (2) dysuria resulting from the passage of urine through a constantly inflamed and irritated posterior urethra producing pain and scalding often accompanied by tenesmus; and (3) the presence in the perineum of a pocket filled with infected residual urine causing a constant feeling of discomfort often described as "resembling a ball of fire," which compels frequent urination in an effort to relieve.



That such diverticula may be overlooked is easily understood if it is realized that the condition is often associated with a normal bladder, as it was in 3 of our cases. Unless an endoscope or a direct cystoscope is used, the floor of the posterior urethra may be overlooked. In Case 1 a cystoscopic examination had been made previous to our examination, and the patient was told that conditions were normal.



FIG. 131.—Lead catheter coiled in a diverticulum of the posterior urethra (Case 1).



FIG. 132.—Bullet and fragments lodged behind the symphysis pubis, and lead catheter inserted into the diverticulum (Case 2).

The etiologic factors in 3 of our 4 cases were the result of former operations for the drainage of infected tissue; in the other 2 the result of spontaneous drainage of abscesses into the urethra.

Case 1. (263163), C. E. M., a single man, aged 33, was admitted to the clinic March 12, 1919. The patient had had gonorrhea four years before, and operations as follows: Drainage of seminal vesicles in 1917, followed by repeated injections of the epididymis on both sides with silver salts; appendectomy June, 1918, and cystostomy December, 1918. He complained of dribbling and frequency. Following the neisserian infection he had tried various forms of treatment without result, and finally had had both seminal vesicles drained with complete relief for three months, when the old symptoms of dysuria, frequency, and perineal pain returned, together with extreme nervousness, loss of weight, weakness, and nausea. His appendix was removed at

this time, and six months later cystostomy with bladder drainage was done, both without relief.

Physical examination disclosed bilateral thickening of the epididymis and of the left vesicle. Analysis of a twenty-four hour specimen of urine showed 900 c.c. with specific gravity of 1030, acid in reaction, a trace of albumin, no sugar, an occasional red blood cell and large amounts of pus. The phenolsulphonephthalein test



FIG. 133.—Lead catheter inserted into diverticulum filled with thorium; bullet fragment lodged behind symphysis.



FIG. 134.—Similar to Figure 133; the diverticulum is filled with thorium, disclosing its extent and relation to the bladder, which is filled with silver iodide.

of the kidney function showed a 60 per cent return of the dye in two hours. X-rays of the kidneys, ureters, and bladder were negative. The systolic blood pressure was 130; the diastolic 90.

Cystoscopic examination revealed a normal bladder with clean urine coming from each meatus and a normal internal urethral sphincter. In the posterior urethra just anterior to the verumontanum was an opening into a diverticulum filled with phosphatic deposit and pus. A lead catheter was coiled in the diverticulum (Fig. 131).<sup>1</sup>

Operation was advised, as we believed that diverticulum in this position, by keeping up a constant source of inflammation about the external sphincter and in the posterior urethra, would account for the dribbling and dysuria, and that it probably was a large factor in the causation of the patient's extreme nervousness.

Case 2. (193464), W. C. S., a married man, aged 36, registered at the clinic May 8, 1917. The patient had had a slight neisserian infection of two weeks duration in 1901, appendectomy in 1900 and an exploration and drainage of the perineum following a rifle bullet wound in 1903. From the date of this wound, when a 22 caliber bullet entered the perineum and lodged behind the symphysis (Fig. 132), he had had constant pain in the bladder; the urethra discharged pus. The pain was exaggerated when the bladder was full or the abdomen was distended; it radiated to the glans penis during micturition.



Fig. 135.—Cystogram of bladder and of diverticulum of the posterior urethra (Case 3).



Fig. 136.—Lead catheters coiled in diverticula of the posterior urethra (Case 4).

Physical examination was negative except for a right inguinal hernia, a perineal scar, and a urethral discharge. The analysis of a twenty-four specimen showed 700 c.c., a specific gravity of 1020, alkaline reaction, a slight trace of albumin, no sugar, and a large amount of pus. The blood examination showed a negative Wassermann, hemoglobin of 77 per cent, 4,500,000 red blood cells, and 6800 white blood cells. Repeated smears of the urethral discharge showed many pus cells but no characteristic Gram-negative diplococci. X-rays of the kidneys, ureters, and bladder were negative except for the presence of the rifle bullet and its fragments (Fig. 132).

Cystoscopic examination showed a normal bladder with clear urine coming from each meatus. The internal urethral sphincter

was normal. In the posterior urethra to the right of the verumontanum was an opening into a diverticulum. Into this a lead catheter was inserted (Fig. 133). The diverticulum was then filled with thorium. Figure 134 shows the extent and position of the diverticulum in relation to the bullet fragments. The diverticulum was evidently the result of the bullet wound, or of the subsequent drainage of the wound, and accounts fully for the painful urination and constant urethral discharge.

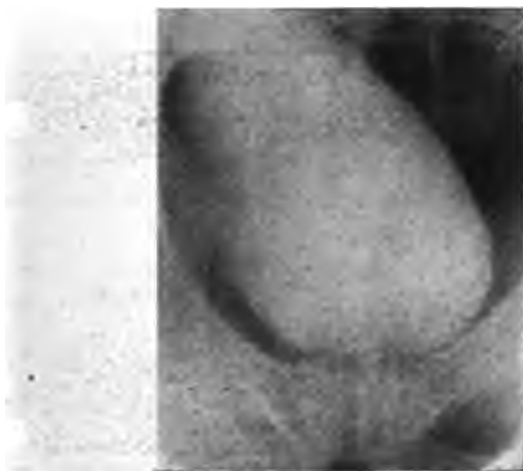


Fig. 137.—Diverticula of posterior urethra filled with thorium, and the bladder filled with silver iodid, showing lax atonic bladder and the relative position of the two diverticula.

Case 3. (214557), F. B., a married man, aged 40, came for examination Nov. 21, 1917. The patient's history was negative except for an axillary abscess seven years before. Following an attack of inflammatory rheumatism four years before, he commenced to have attacks of dysuria which became more and more frequent and were accompanied by frequency and nocturia, all of which grew progressively worse until four months before, when he was obliged to wear a urinal. The passage of urine was attended with great pain and scalding. During the past four years he had lost much weight and strength; he complained of frequent night sweats and chills.

Physical examination revealed many signs of old tuberculous processes in the lungs, and a bar of hard, firm, inflammatory tissue about 4 inches up in the rectum. A twenty-four hour specimen of urine, 1550 c.c., gave a specific gravity of 1009, alkaline reaction, a trace

of albumin, no sugar, many red blood cells, and much pus, stained specimens of which failed to show tuberculosis bacilli. Four guinea pigs were injected with specimens of bladder urine obtained on different days and at necropsy one pig showed miliary tuberculosis foci throughout the peritoneum. The phenolsulphonaphthalein test of kidney functions showed a 35 per cent. return of the dye in two hours. X-rays of the kidneys, ureters, and bladder were negative; x-ray of the chest showed calcified pleurisy at left base and a healed focus of tuberculosis at right apex.

Cystoscopic examination showed a chronic inflammatory tuberculous type of bladder with many areas of granulation tissue and cicatricial changes involving the internal sphincter, which was completely relaxed. On the floor of the posterior urethra just anterior to the verumontanum was an opening into a diverticulum about 3 cm. in diameter. This, together with silver iodid and a cystogram (Fig. 135), shows the diverticulum to be nearly equal in size to the bladder. The diverticulum probably was primarily an abscess in one or both vesicles which ultimately ruptured into the urethra. While the abscess cannot alone be considered the cause for all the present urinary symptoms, since the bladder is so extensively involved, it may well be the etiologic origin of them.

Case 4. (26573, R. L. C., a married man, aged 49, came to the clinic April 1, 1919. The patient had had an operation for multiple bladder and prostatic stones in 1910. He complained of incontinence and perineal pain, and of always having had great difficulty in emptying his bladder, which seemed to lack musculature. Often he was obliged to double himself up and exert pressure suprapubically in order completely to empty the bladder. In 1907 marked bladder irritability commenced, accompanied by dysuria and frequency. In 1910 the perineal operation was performed, and following this sphincter control was lost and he was obliged to wear a urinal. He has also had some difficulty in the control of gas and feces if the bowels are loose.

Physical examination showed a well-developed man of 196 pounds, having a systolic blood pressure of 160, and a diastolic of 100. A transverse perineal scar, and faulty closure of the arches of the sacrum were noted, which the x-ray demonstrated to be a spina bifida occulta. A twenty-four hour specimen of urine showed a specific gravity

of 1020, alkaline reaction, a trace of albumin, no sugar, an occasional red blood cell, and much pus. Blood examination showed 24 mg. of blood urea pus in 100 c.c. of blood. The Wassermann test was negative. X-rays of the kidney, ureters and bladder were negative. Neurologic examination revealed a saddle anesthesia.

Cystoscopic examination showed a large atonic and trabeculated bladder with chronic diffuse cystitis and a relaxed sphincter. In the posterior urethra at either side of the verumontanum were the openings of two diverticula filled with pus and phosphatic deposit. The openings were large enough to permit the coiling of catheters in both at one time, thus giving the impression of a single diverticulum rather than two (Fig. 137). A second plate was made, the bladder having in the meantime been filled with silver iodid, in order to obtain a better idea of the relative position of the diverticula in relation to the bladder (Fig. 137). The diverticula in this case are clearly the cause of the perineal discomfort and explain the expressing of urine by perineal pressure. They are undoubtedly a result of the operation for the removal of bladder and prostatic stones.

#### CONCLUSIONS

1. Diverticula of the posterior urethra are generally of the acquired type.
2. Probably the most frequent etiologic factor is a previous perineal operation.
3. They give rise to a definite syndrome, namely, incontinence, dysuria, interrupted micturition, perineal pain, and pyuria.
4. The absence of a perineal tumor is not incompatible with their presence.
5. Since they may be associated with a normal bladder they may be easily overlooked unless the posterior urethra is carefully examined.

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## THE TREATMENT OF URETHRAL CARUNCLE\*

J. L. CRENSHAW

The varied and often unsatisfactory treatment of urethral caruncles and the high percentage of recurrence after their removal led us to study these growths and the best methods of removing them.

A review of the histories of patients with urethral caruncle who have been referred for examination to the cystoscopic department of the Mayo Clinic during the past four years (April 29, 1915 to June 1, 1919) showed that the symptoms most frequently complained of were urinary frequency, pain and burning on urination, soreness around the meatus, tenesmus, and bleeding. A few patients had no symptoms referable to the caruncle. Cystoscopy was done on all patients with a history of urinary trouble; the findings were usually negative. The nervousness which is a symptom in most of these cases is unquestionably due, in many instances, to the constant irritation in the urethra, since it disappears as soon as the caruncle is removed. In other cases, the nervous symptoms are independent of the caruncle since they persist after its removal. In many instances the inconvenience and suffering seem so out of proportion to the size of the caruncle, that it is often overlooked as the cause of the trouble.

The cases of urethral caruncle observed at the clinic make it possible to draw but one definite conclusion with regard to the etiology. Urethral caruncles seem to be secondary to a chronic irritation or ulceration of the urethral mucosa. Some observers have attributed caruncles to the gonorrheal type of chronic urethritis following directly on gonorrheal ulcerations. The bursting of retention cysts of Skene's glands has also been considered a cause (Englisch). It is probable that chronic irritation from many different causes plays a part in their formation.

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Pathologically, urethral caruncles are of papillomatous outline with either a broad or narrow base growing from the posterior or



FIG. 138.—Exposure of urethral meatus showing urethral caruncle with a single mass on the posterior wall.

lateral walls of the urethra just inside the meatus. I have found only one case of a caruncle on the anterior wall reported in the literature (Neuberger). These growths vary in color from yellowish gray to

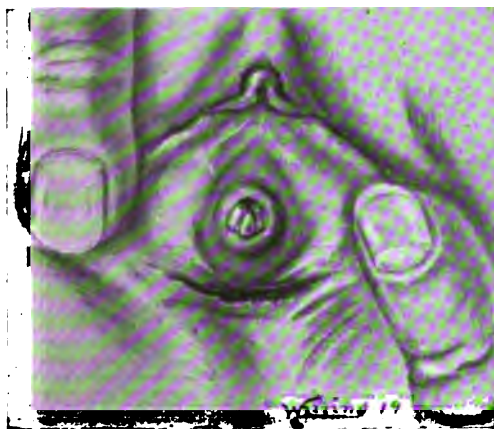


FIG. 139.—Exposure of urethral meatus showing urethral caruncle with posterior and lateral masses.

bright red. Often acute inflammation of the anterior portion of the urethra and tissues surrounding the meatus renders the whole area exquisitely sensitive. Grossly, differential diagnosis of urethral



caruncle and hemorrhoidal growths, urethral cysts, fibromas, prolapse of the urethral mucosa, and malignant growths is often difficult; the



FIG. 140.—Operative technic. Caruncle raised with pick-up forceps and ready to be seized by clamp.

microscopic findings, however, are characteristic, showing the urethra caruncles to be of a uniform structure, composed of loose connective tissue permeated by numerous blood vessels which are often much dilated



FIG. 141.—Operative technic. Caruncle seized in clamp and about to be severed with scissors.

The growth throughout shows marked inflammation, and is infiltrated with mononuclear and polynuclear leukocytes. Many plasma cells are found, especially surrounding the blood vessels. Toward the

free surface the blood vessels are newly formed. The growth is covered by the usual urethral epithelial layer which in areas is thinned



FIG. 142.—Operative technic. Cauterization of stump before removing clamp.

out or absent, leaving an easily bleeding ulcer. Virchow speaks of the normal folds of the urethral meatus as caruncles, designating what we know as caruncles by the term "vascular polyps."

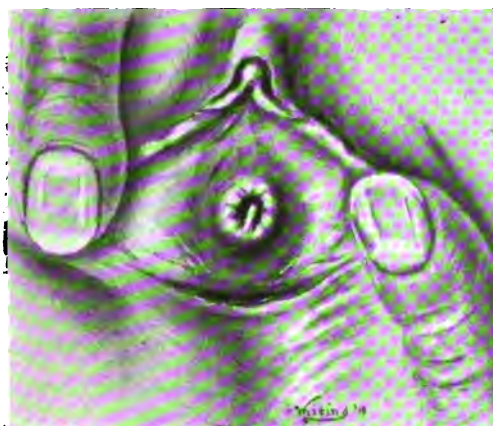


FIG. 143.—Narrow cauterized stump after removing clamp.

Some authors have reported a malignant incidence as high as 25 per cent in the original caruncle and many malignant recurrences.<sup>10</sup> We have not seen a case of malignant recurrence, probably because of the fact that by our method the tissue removed is saved for micro-

scopic examination, and early radical operation is done in all cases in which microscopic section has demonstrated malignancy in the original growth which grossly could not be distinguished from the usual benign caruncle.

In reviewing the literature on urethral caruncle, I find that the removal of these growths has been advised by such methods as excision, actual cautery, various caustic acids, and high frequency



FIG. 144 (Case 169585).—Section of caruncle showing the general outline of the growth at low magnification.

current.<sup>1, 3, 4, 6, 7, 9</sup> Most articles record the fact that a recurrence is frequent and with it a recurrence of the original symptoms.

Recurrences have been divided, on the basis of our experience, into two classifications: First, true recurrence of the caruncle due to incomplete removal of the base, and second, prolapse of the mucous membrane of the urethra due to the contraction of the scar following the removal of the original caruncle. The majority of so-called recurrences belong to the prolapse group; they involve a portion or all the circumference of the urethra proportionate to the extent of the

original scar. A removal of this prolapse by any method merely results in a larger scar and in a repetition of the prolapse. We have seen several cases following removal of a caruncle and subsequently repeated removals of prolapsed mucosa in which the mucosa of the trigone was dragged down into the urethra and even protruded from the meatus. The many patients with recurrences of the second type, prolapse of the mucosa, who have consulted us and for whom permanent



FIG. 145 (Case 169585).—Caruncle showing the characteristic structure and epithelia covering. ( $\times 50$ .)

relief was impossible led us, four years ago, to adopt our present form of procedure which has proved very satisfactory. The steps in the method are as follows:

1. The patient is placed in the lithotomy position, and the parts are thoroughly cleansed with soap and water. A swab of cotton on a toothpick saturated in 10 per cent cocain solution and lubricated with a soluble lubricant is inserted into the urethra and left for ten minutes.

2. The labia are separated by an assistant. On examination the caruncle is found to consist either of a single tag on the posterior wall or of posterior and lateral masses. Each tag is picked up with a small Graefe fixation forceps and clamped off in the long axis of the urethra with a special clamp which has a broad blade and a narrow crushing edge. Care is taken to include in the bite all the caruncle and none of the submucosal structure of the urethra.



FIG. 146 (Case 169585).—Section of caruncle shown in Figure 145. ( $\times 100$ ).

3. The growth is cut off close to the upper surface of the clamp; the crushing of the pedicle prevents all bleeding and makes an accurate removal possible. The specimen is saved for microscopic study.

4. The cut surface is thoroughly seared with acid nitrate of mercury solution applied with a wooden applicator. An excess of the acid to run over the blades of the clamp and cauterize other areas of the urethral mucosa is cautiously avoided.

All tags are removed in the same manner; when removal is complete one or more narrow longitudinal white lines about 1 cm. by 1 mm.

mark the cauterized tissue; these lines are separated by normal mucosa. Within a week all evidence of the operation disappears. The advantages of this method of removal of urethral caruncles are:

1. The entire growth can be removed at a single operation.
2. The operation can be done without pain under local anesthesia.
3. Bleeding does not obscure the field during the operation nor annoy the patient afterward; the operator may be sure, therefore, that all the growth has been removed and recurrences thus avoided.
4. There is a minimum of scar tissue since there is no sloughing as the destruction of tissue is absolutely under control. The small amount of scar tissue remaining is in longitudinal lines and separated by islands of healthy mucosa so that a postoperative prolapse of the mucosa due to contraction of the scar does not occur.
5. Symptoms are relieved almost immediately.
6. The specimen removed is not destroyed and may be sectioned for microscopic study.

During the past four years 118 patients have been treated by this method; so far we have learned of only four recurrences.

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## DISEASES AND TREATMENT OF THE PROSTATE GLAND\*

E. S. JUDD.

The prostate gland is a part of the generative system and its function is that of secreting a substance which acts as a sustainer and carrier medium for the spermatozoa. The gland is developed from several series of embryonic buds which form its several lobes. The activity of the gland is confined to adult life; during that time it is seldom subject to any pathologic processes requiring surgical treatment. An inflammatory process, frequently associated with a specific infection in other parts of the genito-urinary system, may occur and at times may progress to the point of suppuration, although this condition is rare compared with the frequency of infections elsewhere in the body.

Tuberculosis may also involve the prostate during early adult life either as a primary focus in the gland or secondary to a lesion in the epididymis or kidney. The question of whether tuberculosis of the prostate should be treated surgically has been widely discussed, because of the fact that when the condition occurs as a secondary process it usually subsides after the primary focus has been removed.

Several years ago Alexander advocated the removal of the inflammatory lesion when it is associated with specific infection, but this opinion has not received general approval, largely, I believe, because most patients recover from the ordinary, conservative procedure. It may, therefore, be said that except in cases of suppurating inflammatory processes it will seldom be advisable or necessary to operate on the prostate during early adult life.

The prostate gland is of special interest surgically at the period in which it is becoming physiologically inactive. At this time the pathologic condition which very commonly occurs in the gland, adenoma, which is so peculiar to it, begins to develop. This so-called adenomatous hypertrophy is probably present in almost all men past

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Reprinted from Jour. Mich. State Med. Soc., 1919, xviii, 469.

55, although it produces symptoms only in persons in whom the enlargement interferes in some manner with the mechanism of urination. Usually the first change that is noticed is urination during the night, and this may be the only indication. I am firmly convinced after careful questioning and after studying the condition of men who come for examination for various complaints at this time of life, that most men who reach 55 to 60 have some enlargement of the prostate. This is evidenced by frequency of urination or by enlargement or change in the prostate which may be discovered on rectal examination.

Prostatic hypertrophy has often been attributed to some infection resulting in urgency, frequency, and difficulty of urination. Usually these symptoms first appear at intervals, later they become more frequent, and finally they are continuous. Complete retention which may occur early in the course of the trouble is often associated with some other condition such as an infection in the form of a cold in the nasopharynx. Ordinarily the first symptoms are not at all serious and may cause little if any inconvenience. Before long, however, incomplete emptying of the bladder and an increasing amount of residual urine becomes evident. This condition, with its resultant changes, is the most serious feature to be considered in dealing with these cases. Just how these secondary changes are brought about has not been definitely shown, although it is well understood that with the increase of symptoms and the amount of residual urine the disturbance in the functioning capacity of the kidneys increases. This change in the equilibrium may be so gradual that the patient is scarcely aware of his condition while in reality through gradually diminished kidney function, he has almost reached the uremic state. The decrease in renal function may be most marked in cases in which the local bladder symptoms are not pronounced; in dealing with the condition this point must be thoroughly understood in order to avoid unpleasant surprises. Because of this much stress has been laid on the importance of preoperative treatment by those who have had the largest experience. Patients with uremia do not withstand operations well; the tendency to uremia must be overcome before any surgical procedure should be considered. Not all patients reach this state before they come for consultation and therefore all patients do not require preoperative treatment, but if the amount of residual urine is considerable and the kidney function is reduced, preoperative treatment is certainly most important; it not only changes postoperative



convalescence and complications but also very greatly reduces the mortality following operation. All credit is due the laboratory worker for devising an accurate method of determining the renal function, for by these tests we are able to follow cases through the preparatory stage and to determine definitely when the function has returned sufficiently to make surgical treatment safe. The general physical state of the patient is of great importance as other considerations, aside from diminished renal function, may contra-indicate any operative work. In my opinion, an estimate of the blood urea is necessary; if the urea is excessive any operative procedure is contra-indicated even if all other findings seem to show that conditions are satisfactory.

During the preoperative care which consists in carrying the patient through the state of reaction following the withdrawal of residual urine by a urethral catheter, or by a suprapubic drain, a perfectly characteristic reactionary condition occurs. The patient becomes weak, is unable to sleep or rest, is very nervous, loses weight, and is altogether miserable. The specific gravity of the urine drops; the phenolsulphonephthalein output and blood urea are often evidence of disturbed renal function. The reaction usually subsides in two or three weeks although it may require much more time. At this stage of the treatment the patient is in much better condition than he has been for years and the obstructing prostate is removed purely for the relief of the mechanical disturbance in the urethra and bladder. I emphasize these general changes in the patient with adenomatous hypertrophy of the prostate since they are characteristic of this type of case, probably because the condition produces more mechanical disturbance than some of the other pathologic processes which must be considered.

In contrast to the inflammatory prostatic changes occurring in younger men, which are not ordinarily considered surgical, is the inflammatory prostatic disease occurring in older men which is more often benefited by surgery than by any other form of treatment. Possibly the prostatitis of older men is a continuation of an earlier process; sometimes the history of the case will bear this out, although a distinct group of persons who have definite prostatitis after middle life present no history nor evidence of an inflammatory process in early life. This condition is sometimes described as a prostatic bar or a small hard prostate. In some instances calculi are deposited within the gland acini and a calcareous prostatitis is the result.

Frequently a marked cystitis and at times a pyelonephritis, possibly an old inflammatory process in the epididymis and testicles, are associated with the condition. The bladder is usually inflamed, trabeculated and thick-walled, and may contain one or more diverticula. The patient complains of considerable pain in the perineum and of symptoms of cystitis. Usually there is not a great amount of residual urine. Such patients require preoperative treatment not primarily because of the residual urine, but to clear up the infection as much as possible. Frequently local treatment with prostatic massage is given, but in our experience permanent relief is not often obtained; much greater benefit follows suprapubic removal of the inflammatory tissue. The transvesical operation is especially indicated in these cases as it is difficult to remove the inflammatory scar tissue, and the sphincter muscle may be injured if the perineal operation is employed. Chronic prostatitis, with or without calculi, does not receive the consideration from a surgical standpoint which I believe it deserves. Temporary relief in these cases is obtained by conservative methods of treatment, but all the symptoms return when the treatment is stopped. In most instances complete and permanent relief will be assured by the more radical surgical measures.

Another condition frequently associated with pathologic changes in the prostate is diverticulum of the bladder. I am convinced that the condition occurs more frequently than we have supposed and that we will recognize the condition much more often if we are on the lookout for it. Many of the cases of so-called protracted cystitis not relieved by prostatectomy are really cases of diverticulum of the bladder. In any case in which there is a great deal of infection in the bladder and especially if the cystitis is of the foul smelling type we may expect to find a diverticulum, and only by the removal of the diverticular sac as well as the prostatic obstruction will complete relief be afforded. Removal of the obstruction and drainage of the diverticulum will not suffice.

The present results of the surgical treatment of malignant disease of the prostate are not gratifying. This condition differs entirely from other pathologic lesions in the gland especially since it almost invariably originates in the small posterior lobe of the gland and its extension is upward beneath the bladder and between the seminal vesicles before it involves other parts of the prostate or the bladder itself. For this reason the disease may become quite extensive before

any urinary symptoms are noted. Many cases are on record in which a carcinoma of the prostate has been known to exist for a number of years without producing symptoms. I have observed several untreated patients over a period of more than five years who were in comparative comfort.

In view of the fact that cancer of the prostate originates in the posterior lobe in close association with the anterior part of the rectum; that the disease is an infiltrating process which is not encapsulated and a complete removal of all sphincter control of the bladder is necessary thoroughly to eradicate the disease; that the cancer in itself may exist for some time without producing much if any discomfort; and that radium applied by the radium needles will probably greatly prolong the period so that the patient may live many years in comfort, it is probably best to consider cancer of the prostate as not satisfactorily amenable to radical surgical procedures. A certain number of patients with cancer of the prostate have difficulty with urination, and this may be due to the enlargement of the cancer or more likely, to an associated adenomatous hypertrophy. In either event if there are no other contra-indications it is advisable to remove the adenomatous enlargement or enough of it so that urine may be expelled easily; the operation should be followed by radium treatment. Cancer of the prostate, we believe, should be operated on only when it interferes with urination; our results, both with regard to the comfort and the convalescence of the patient following radical operation do not warrant its employment. Some patients are undoubtedly greatly benefited by radium.

Regarding the technic of the operation for the removal of enlargements in the prostate: We are endeavoring to take the operation from the realms of the rather blind and rapidly performed operation to one performed as much as possible under the guidance of the eye with a technic as definite and accurate as that of any abdominal operation. It is difficult in all patients to expose the prostatic region, and especially in those who have been operated on before. In the great majority of cases the area can be brought into view, however, so that the operation may be carried out very accurately. The entire enlargement can be enucleated and any tags removed. Bleeding, which is one of the most important features in the technic, can usually be absolutely controlled in doing the open operation. In many instances the bleeding comes from a single vessel and a single ligature will

make the field dry. The old idea that the loss of blood is good for such a patient, no longer holds. There is less tendency to infection in the open operation; the tissues are protected and less traumatized. The operation of prostatectomy must be considered a major operation and, as in other operations of this degree, the more accurate the technic the more satisfactory will be the result.

## THE OPERATIVE TREATMENT OF VESICOVAGINAL FISTULA\*

E. S. JUDD

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Fistulas between the bladder and the vagina are the result of difficult parturition, or some operative procedure, most often extirpation of the uterus for cancer. In the early days most of the cases of fistula that were under observation were the result of trauma at the time of childbirth. It was in the treatment of such cases that Sims developed the first accurate operative technic for their repair. In later years, however, several factors have arisen to change conditions materially. In the first place, better obstetric management has greatly reduced the number of fistulas which occur as the result of difficult labor, but there has been a great general wave for the radical extirpation of cancer both by operative procedure and by cautious and large doses of radium. While the ultimate results of these operations and treatment warrant the procedure they very greatly increase the number of cases of vesicovaginal fistula. Sampson, in 1908, reported 19 cases following 158 hysterectomies for carcinoma of the cervix, while a review of the cases in which we have operated since 1908 shows that 61 per cent of our cases have resulted from some operative procedure for the removal of tumors of the uterus, and only 39 per cent followed childbirth. These percentages undoubtedly would be different in a strictly obstetric and gynecologic clinic, but they indicate the cause of the fistulas which are generally seen.

The occasional satisfactory result of the treatment of a carcinoma of the cervix which is extensive and involves the vaginal mucous membrane undoubtedly warrants the continuance of treatment in such cases. The apparent complete disappearance of a large cauliflower carcinoma of the cervix after a few treatments with radium is most striking, but these treatments should not be undertaken without consideration of the fact that a fistula from the bladder may result from the use

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Reprinted from *Surg. Gynec. and Obst.*, 1920, xxx, 447-553.

radium alone as well as from operation or cautery. If the malignancy is eradicated so that the fistula may be repaired satisfactorily the operation is certainly justified, but if the patient is left without control of the urine and with malignancy persisting in the edges of the fistula or evident in other places, the treatment cannot be justified. For this reason the extent of involvement must be studied carefully to make sure that the patient has some chance of relief before the additional risk is taken. Radium has been a great help in the treatment of cancer of the cervix and ordinarily it can be used without the danger of injury to the bladder, although there are 5 cases in our series in which the fistulas followed the use of radium alone.

The scar resulting from the cautery or radium renders the technic of the operation much more difficult than in the cases which follow childbirth. The scar from the use of the cautery is thick and firm and it is very troublesome to free the tissues so that the flaps may be approximated and sutured. The flaps tear readily so that care must be taken in forcing the needle through them. The scar resulting from the trauma of parturition is much smaller and the tissues are much more pliable and easier to suture.

The apparent ease with which vesicovaginal fistulas may be closed is sometimes deceiving and, unless definite principles are followed, the results will not be uniformly satisfactory. Too many times, I believe, an attempt is made to close the opening before dissecting the bladder wall well away from the vaginal wall. In some instances it may be possible to close the opening in this manner, but I agree with recent writers on the subject who emphasize the fact that the underlying principle of the technic of the operation is the separation of the wall of the bladder from the wall of the vagina. The condition which keeps the fistula from healing of its own accord is the fact that the mucous membrane of the bladder and vaginal wall have healed together, thus forming a continuous mucous membrane surface from the bladder to the vagina. The first essential in the treatment consists in destroying the communication, and the best manner of accomplishing this is to dissect the bladder completely away from the vagina as is done in the operation for the relief of cystocele. If the mucous membrane of the fistulous tract is not freed so that it can be turned into the bladder on the one side and into the vagina on the other the communication will almost certainly reform. A review of our cases shows that often several operations have been necessary

before the fistula closed permanently. Sixty-eight per cent of our patients had been operated on before coming to the clinic from one to seven times. In most instances these operations had apparently been done well; in others I believe the operator had been deceived into performing an operation by its apparent simplicity. Undoubtedly a certain percentage of these patients require more than one operation, and I believe we are justified in repeatedly attempting to try to close the fistula if the sphincter muscle has not been destroyed. If the urethra and the sphincter muscle are destroyed there is nothing to be gained in operating to close the fistula as the urine will continue to escape. At times the urethra may be destroyed and the sphincter be intact; in these cases the operation should be performed as the absence of the urethra will not cause any great inconvenience. In other cases the sphincter may be divided or torn by trauma and there is every likelihood that the sphincter will functionate if it is repaired; therefore operation to close the fistula and repair the sphincter should be done. It seems to me that the operability of these cases depends on whether or not there is a sphincter muscle. Even though it is severed any number of attempts should be made to repair it before the only other feasible procedure is advised, that is, some plan of diverting the urine to the rectum, thereby leaving it under the control of the rectal sphincter; this may be done if the sphincter of the bladder is completely destroyed. Probably Keen's plan is the best one to adopt in these unfortunate cases, that is, to make a large communication between the vagina and rectum just above the anal sphincter and then close the vaginal outlet. In Keen's case the woman defecated and urinated for more than thirty-five years and menstruated for eleven years by rectum. Peterson collected 41 cases in which this operation was performed with comparative success. In one case only the patient died of a kidney infection and that was some months after the operation; the infection was not believed to be due to the entrance of organisms from the colon to the bladder.

The basis of this review is the 78 cases in which operation was done in our clinic from January, 1908 to September, 1919.\* In 54 of these cases it was possible to close the fistula at one operation; in 16 two operations were performed and in 1 six operations failed completely to close the fistula. The size of the fistulous opening in these cases

\* I am greatly indebted to Dr. R. G. Andres for his careful study of our case records and the resulting data.

varied from the size of a small pin-point to complete eversion and prolapse of the bladder. Complete prolapse of the bladder into the vagina occurred in 2 cases, one following childbirth in which several operations had formerly been done, and one following combined cautery and radium treatment for cancer of the cervix. In the first case the fistula was repaired successfully, but in the second case the repair was not complete; the entire anterior part of the rectum had been destroyed by the use of the cautery, and it was impossible to keep the field of operation clean.

In 75 cases the fistulous opening was single; in the other 3 cases there was more than one opening. The multiple fistulas did not offer any more difficulties than the single. A large incision in the vaginal wall included all the openings and converted the operation into a single closure after the openings into the bladder had been separately closed.

The bladder sphincter was involved in 10 cases, but it was destroyed in only 3; it was repaired quite satisfactorily in the 7 cases.

One of the ureters was involved with the vesical fistula in 6 cases. I believe that it is very important to determine the relationship of the ureters whenever it is possible. In a few instances the opening of the ureter was found close to the edge of the fistula and it was possible to turn it into the bladder, or at least avoid injuring it. In several of the cases in which the ureter was involved the suprapubic operation was performed; the ureter was transplanted if it appeared to be in good condition, and the opening of the vesical fistula closed. In one of these cases the ureter was thickened and evidently had been completely occluded for a long time so that it seemed advisable to ligate it.

In all cases in which the suprapubic operation was selected it was selected for some special reason; it was not employed generally in vesicovaginal cases. The patients on whom the suprapubic operation was performed have all done well, and their convalescence was more favorable than might have been expected. While the suprapubic operation offers a good chance for cure, it also offers a greater opportunity for infection, and should not, therefore, be chosen unless especially indicated. Our suprapubic operations were performed extraperitoneally.

Trendelenburg, is credited with having performed the first suprapubic operation for vesicovaginal fistula in 1890, and, according to Ward, there were 27 of these operations reported within the next four-



teen years. Fewer operations have been reported during the past fifteen years, probably on account of the added risk of infection.

Legueu has recently advocated the transperitoneal vesical route for vesicovaginal fistula. One of his 12 patients operated on by this method died. He claims for this method wide exposure and every security for healing since in making closure the bladder incision is

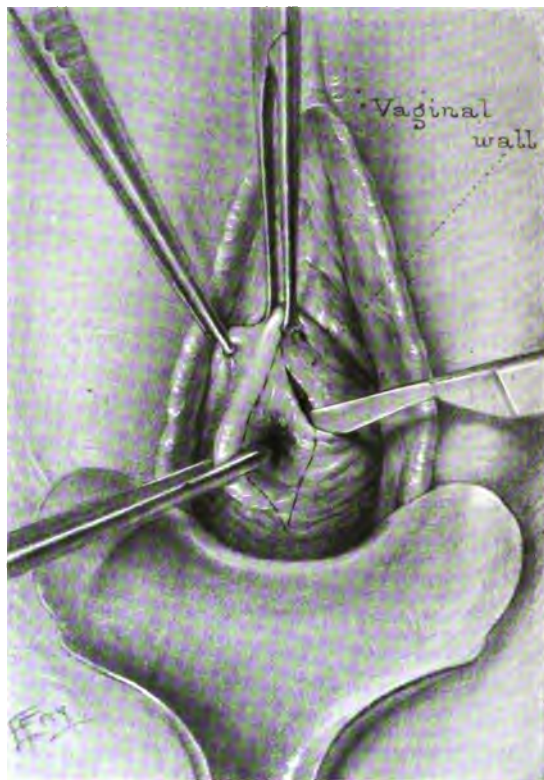


FIG. 147.—Dotted line indicating area around fistula to be incised.

covered by peritoneum. Such suprapubic operations undoubtedly should be carried out in some of the very bad cases, especially if the ureter and bladder are traumatized. In certain instances the fistulous tract becomes attached to the pubic bone and is thus held in a most inaccessible position, making closure difficult by the vaginal route. In some of these cases the suprapubic operation can be used to advantage.

In most instances cases of vesicovaginal fistula can be dealt with satisfactorily by making plastic closure of the fistulous opening

through a vaginal incision. If the opening is small the technic described by C. H. Mayo may be followed, that is, inverting the fistula into the bladder. The inverted fistula is held in the bladder by tension on the purse string suture which is pulled out through the urethra.

Crenshaw, of our staff, has closed a number of small vesicovaginal fistulas by the use of the high frequency current. If the fistula is small it is well worth while to try this method before attempting an operation.

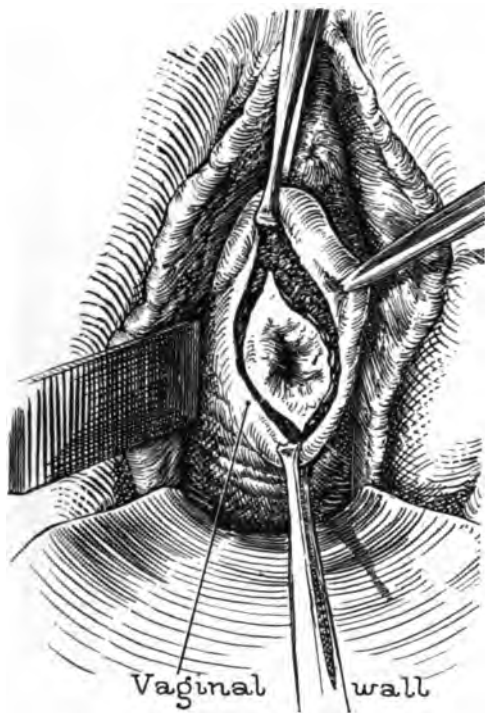


FIG. 148.—Incision completed and vaginal wall retracted.

Before any operation is undertaken an effort must be made to get the tissue in the best possible condition for healing. This frequently requires several weeks since often the mucous membrane of the vagina and of the labia, and even the skin of the thighs are excoriated and infected, and contain deposits of salts. A cystoscopic examination should always be made in order to determine the position of the ureters, the presence or absence of a sphincter muscle, and whether or not the

bladder is completely severed from the urethra. One of the greatest difficulties encountered is trauma to the vesical neck. The vaginal operation certainly should be chosen in all cases of injury near the neck of the bladder, the part difficult to expose by suprapubic incision so that in such injuries this incision would be distinctly contraindicated. If the opening in the bladder is high in the vaginal fornix and especially if there is much scar tissue, as there is apt to be following

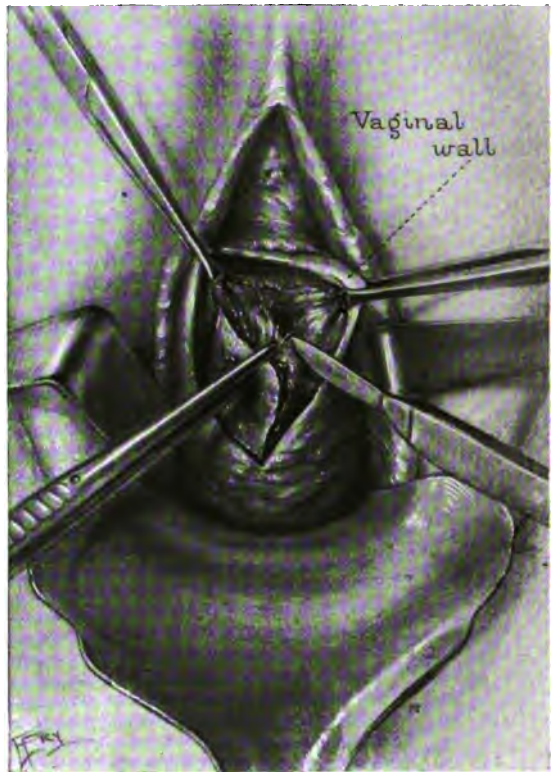


FIG. 149.—Dissection of the wall of the vagina from the wall of the bladder.

cautery or total hysterectomy, it will be difficult to obtain sufficient exposure by vaginal incision and in some instances it may seem best to perform the suprapubic operation. The fistula can usually be made accessible, however, so that the operation may be done through the vagina. Very often the perineum is badly torn, and incision into it for exposure is not necessary, but if the incision is necessary it should be made unhesitatingly and the openings closed at the completion of

the operation. One of the chief steps in this procedure is a long incision in the vaginal wall down to the bladder. Usually the incision is begun immediately below the sphincter muscle and extended to and through the fistulous opening, after which the bladder is separated from the vagina for a considerable distance (Fig. 147). I have found it easier to begin this dissection as near the cervix as possible and to bring it forward toward the urethra. Unless this step is thoroughly

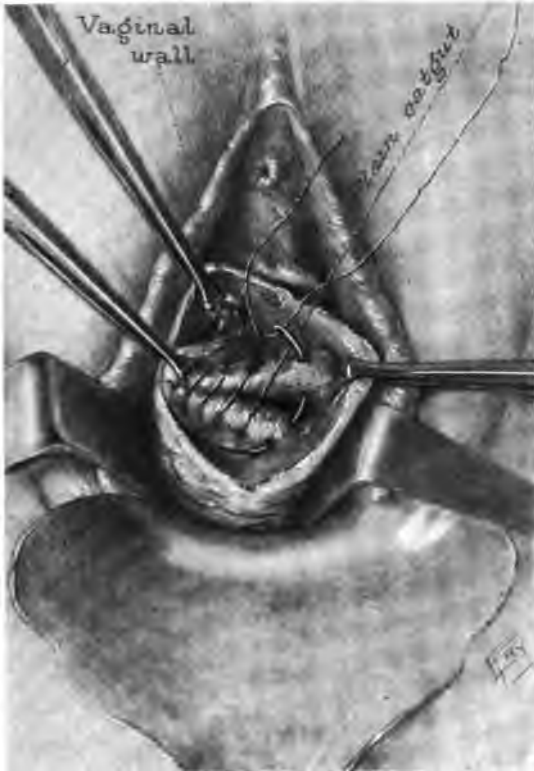


FIG. 150.—Suturing the wall of the bladder.

carried out the chance for a cure is not good. If the cervix has not been removed it should be tracted downward as this helps materially in the exposure (Fig. 148). If the cervix has been removed and the fistula is high in the vagina it may be best to open the peritoneum widely in order freely to mobilize the bladder and bring the fistula into view. Several years ago Kelly suggested opening the peritoneum and I have followed this method a number of times to great advantage.

It must be remembered that loops of intestine are usually caught in this scar and are apt to be injured. This accident happened in one of my operations, but I was able to repair the opening in the intestine without much trouble. Ordinarily I do not believe that it is necessary to open the peritoneum, but in almost inaccessible cases it is helpful. Slight infection may follow, although it was not a complication in

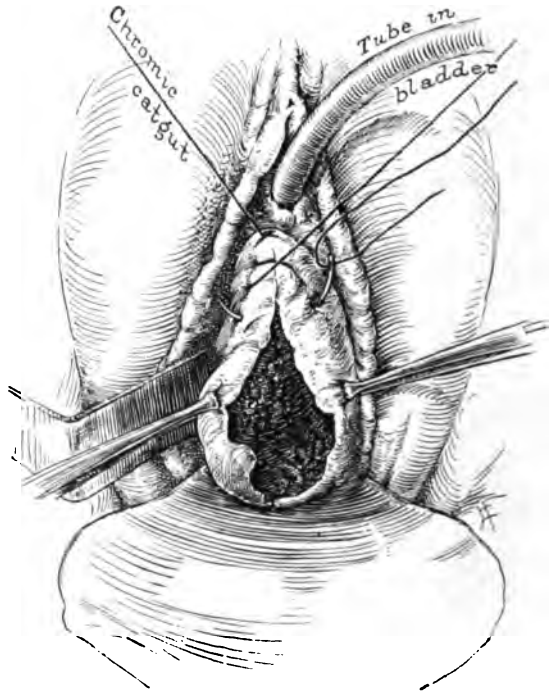


FIG. 151.—Suturing the wall of the vagina.

my cases. In one case in which I did not open the peritoneum the patient developed a fecal fistula through the vagina several days afterward, and I was obliged to repair it by abdominal procedure.

A small curved hemostat passed through the urethra and into the vagina through the fistula has helped us most to bring the fistulous tract downward into the dissection. The dissection of the bladder should be carried on until the wall is loose and free and until the edges can be easily approximated (Fig. 149). In the cases of extensive injury this is sometimes impossible and it then seems best to close the

bladder opening as completely as possible without using tension on the sutures; complete closure can be made later. If too much dissection and tension is employed the circulation to the flaps will be reduced, and sloughing of the tissues will occur. Fortunately many of the flaps may be separated without harm. It is better to perform two or three operations than to carry the procedure too far at one time. The opening in the bladder should be closed with catgut and the

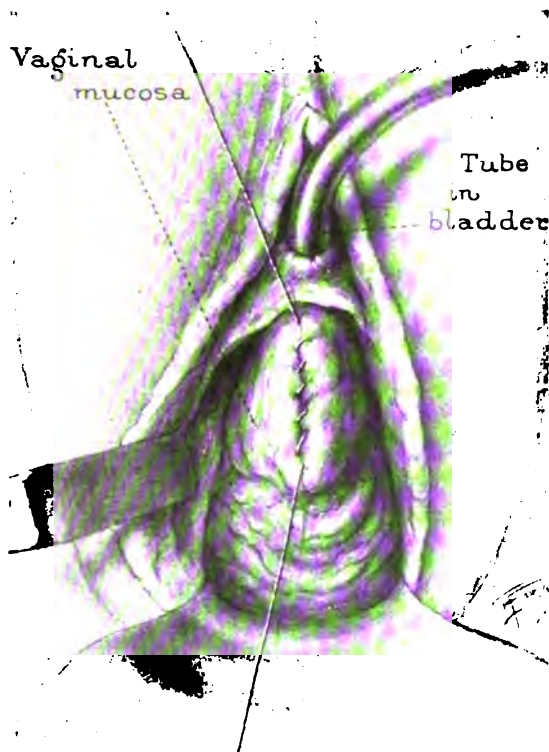


FIG. 152.—Closure of the wall of the vagina.

of the mucous membrane inverted (Fig. 150). The vaginal opening should be closed with chromic catgut and all dead space between the bladder and vagina obliterated (Figs. 151 and 152). If the sphincter has been repaired or the urethra sutured back to the bladder it is best to use fine silk sutures in addition to the catgut, being cautious not to penetrate the mucous membrane with the silk. A retention catheter is left in the bladder for from eight to ten days,

and great care must be taken to make sure that it drains properly. Patients should be kept quiet for from twelve days to two weeks.

There was no mortality in this series of cases, and the ultimate results were very satisfactory in a large percentage. We have recently received information concerning 56 of the 78 patients. Four state that they have derived no benefit from the operation; 6 are considerably improved, although there is still slight incontinence of urine. All the other patients are completely relieved and the bladder function is normal.

In conclusion I wish to emphasize points as follows:

1. Vesicovaginal fistulas are now more common following operations than following childbirth.

2. All vesicovaginal fistulas should be considered operable as long as the sphincter muscle of the bladder is intact or can be repaired. If the sphincter has been completely destroyed it will be necessary to consider some other procedure.

3. Suprapubic extraperitoneal operations seem to be indicated if the cystoscopic examination reveals injury to a ureter as well as to the bladder, or it may be indicated if the fistulous tract is adherent to the pubic bone.

4. The plastic vaginal operation consists in completely separating the bladder from the vagina and closing the two separately and obliterating all dead space.

5. A large percentage of complete and permanent cures follows such operations.

TABLE 1.—TYPE OF URINARY FISTULAS OPERATED ON FROM JANUARY, 1908 TO SEPTEMBER, 1919

Cases.....	82
Vesicovaginal.....	67
Vesico-ureterovaginal.....	6
Vesico-uretero-uterine.....	1
Vesico-utero-vaginal.....	5
Vesico-urethro-vaginal.....	3
Age of youngest patient.....	19 years
Age of oldest patient.....	64 years

TABLE 2.—CAUSES OF FISTULAS

	Cases
Childbirth.....	32 (39 per cent)
Operation.....	50 (61 per cent)

TYPE OF OPERATION

Hysterectomy.....	31 (13 in our clinic)
Percy cautery (no hysterectomy).....	4 ( 2 in our clinic)
Excision of cervical stump.....	3
Percy cautery and radium for recurring cancer (previous hysterectomy).....	3 ( 2 in our clinic)
Amputation of cervix.....	2
Lithopaxy through urethra.....	2
Puncture drainage of bladder for cystitis.....	3
Abscess drained through vagina.....	2
	<hr/>
	50 (17 in our clinic)
Shortest time between occurrence and repair.....	3 weeks
Longest time between occurrence and repair.....	24 years

TABLE 3.—OPERATIONS PERFORMED ELSEWHERE

Repair attempted before coming to clinic in.....	44 cases
13 patients had had 1 operation	
15 patients had had 2 operations	
6 patients had had 3 operations	
4 patients had had 4 operations	
3 patients had had 5 operations	
2 patients had had 6 operations	
1 patient had had 7 operations	
No previous operation for repair of the fistulas.....	38 cases

TABLE 4.—PATIENTS OPERATED ON IN THE CLINIC, 78

54 patients had 1 operation	
16 patients had 2 operations	
4 patients had 3 operations	
1 patient had 4 operations	
2 patients had 5 operations	
1 patient had 6 operations	
Inoperable recurring carcinoma of the bladder ruled out plastic operation in.....	4 cases
The fistulas varied from a very small opening to complete eversion and prolapse of the bladder.	

TABLE 5.—EXTENT OF INVOLVEMENT

	Cases
Bladder sphincter.....	10
Bladder sphincter completely destroyed.....	3
Ureter.....	6
Single fistulas.....	79
Multiple fistulas.....	3

TABLE 6.—TYPE OF OPERATION

Plastic closure	{ Layer suture	
	{ Dissection of fistulous tract and closure	69 cases
	{ Inversion of edges by tension through meatus	
Suprapubic operation.....		5
Transplantation of the ureter.....		3
Ligation of ureter.....		1



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## ECTOPIC ADENOMYOMA OF UTERINE TYPE (A REPORT OF TEN CASES)\*

A. E. MAHLE AND WM. CARPENTER MACCARTY

It is evident, regardless of the amount of literature which has been written on the subject, that the importance of adenomyoma has not been recognized either clinically or surgically.

Adenomyomas of the uterus and tubes and those extending into the broad ligament were described before 1894 by Babes, Breus, Diesterweg, and others. In 1896 von Recklinghausen's complete work, *Die Adenomyome und Cyst-adenomyome der Uterus und Tubenwandung* appeared. Adenomyomas of the round ligament, ovarian ligament, rectovaginal septum, and ovary<sup>14</sup> were reported in the latter part of the nineteenth century. So-called adenomyomas occur also in the stomach and intestines, and have been described in the kidney and gallbladder. In the latter cases, the glandular elements resemble those of the tissue in which they are found.

Cullen, in 1908, in his book, *Adenomyoma of the Uterus*, published a review of 83 cases of adenomyoma occurring in 1283 cases of fibromyomas of the uterus, about 5.7 per cent of all the cases. In 1919, MacCarty and Blackman reported a total of 211 cases of adenomyoma in 3398 fibromyomas of the uterus, 6.43 per cent of all the cases.

In 1916, Cullen published his comprehensive work, *The Umbilicus and Its Diseases*, in which he collected all the cases of adenomyoma of the umbilicus reported up to that time, 13 in number. In his opinion, it was doubtful whether 4 of these cases should be included in the group.

The 10 cases herewith reported were extra-uterine and extratubal tumors, diagnosed at the time of operation as adenomyomas. These growths contained glandular portions resembling typical uterine mucosa, surrounded by a fibrous connective tissue, and smooth muscle stroma, the latter in varying amounts. The distribution of the tumors was as follows: Umbilicus 1, abdominal wall 2, sigmoid 1, groin 2, and rectovaginal septum 4.

\* Reprinted from Jour. Lab. and Clin. Med., 1920, v, 218-228.

## ADENOMYOMA OF THE UMBILICUS

CASE 1.—This patient, aged 42, had been married for twenty-three years, during which time she had been pregnant four times, the last pregnancy occurring thirteen years before. She had noticed a growth in the "navel" four years before, but it had disappeared until several months before examination. At this time she noticed a hard, bluish tumor, which seemed to be growing larger, "broke open," and discharged a bloody serous fluid. The tumor became quite painful at the time of menstruation.

On examination, the enlargement was found, as described, with bluish areas beneath an intact epidermis, and, clinically, it was considered a "suspicious tumor." Excision of the tumor was followed by a Mayo operation for umbilical hernia. The tumor had no connection with the peritoneum or any abdominal viscus. (Figs. 154, 160 and 161.)

Some patients in the cases of adenomyoma of the umbilicus reported by Cullen gave a history of enlargement of the tumor at the time of menstruation, and one patient noticed a bloody, serous discharge which occurred during catamenia. This author, because of the very close resemblance, pathologically, of these tumors to adenomyoma of the uterus, believes them to have originated from misplaced uterine mucosa or from remnants of Müller's ducts. Goddard, in 1909, expressed the same opinion. While this may be correct, we believe that up to the present time no conclusive evidence has been offered, and that the real origin of these tumors is not positively known. Of the cases which have been reported previously, all have been cured by simple excision of the tumor. Our patient, who was operated on quite recently, has been relieved of all symptoms, but not sufficient time has elapsed to assure a permanent cure.

## ADENOMYOMA OF THE ABDOMINAL WALL

The two patients with adenomyoma of the abdominal wall had been operated on elsewhere for retroversion of the uterus, for which one had an internal shortening of the round ligaments, and the other a ventral suspension.

CASE 2.—This patient, aged 30, complained of a tender lump, of two years' duration, in the lower abdominal wall, under a previous laparotomy scar. The lump was painful at the time of menstruation.

On examination a palpable mass, 3 cm. in diameter, was found beneath the lower end of a median laparotomy scar; this was hard, nodular, and painful to the touch. It was apparently not attached to the uterus, and, clinically, was thought to be a fibrous tumor in a previous laparotomy wound.

At operation, the mass was removed; it extended through the abdominal muscles, and was attached to the left tube about 4 cm. from the uterine horn. (Figs. 153, 162, 163, 164 and 165.)



FIG. 153 (Case 2, 251296).—Adenomyoma of tube and abdominal wall. The thickened portion of tube (adenomyoma, Fig. 262) was adherent to adenomyoma of abdominal wall. (Fig. 163.)



FIG. 154.

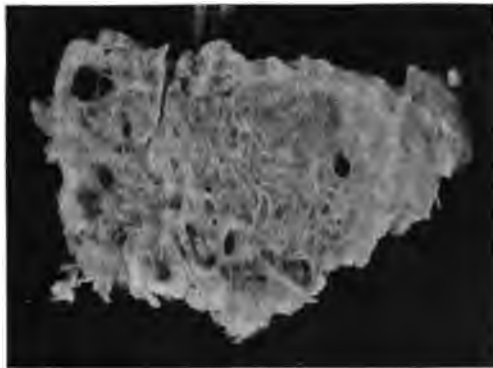


FIG. 155.

FIG. 154 (Case 1, 261880).—Adenomyoma of the umbilicus cut in cross sections, showing small cystic areas filled with dark brown pigment.

FIG. 155 (Case 3, 177844).—Adenomyoma of the abdominal wall with white fibrous bands of connective tissue extending through substance of tumor with cystic areas filled with dark brown pigment.



FIG. 156 (Case 5, 109474).—Adenomyoma of the groin.

**CASE 3.**—This patient, aged 46, had had a ventral suspension performed several years before and had been pregnant nine times, the last pregnancy occurring ten years before. She complained of lumps in the abdominal wall, which she had noticed for the last year. These lumps had not grown noticeably larger, but were always painful following menstruation.

On examination, a mass was found in the suprapubic region, apparently in the abdominal wall, movable with it, and possibly connected with the fundus of the uterus. Clinically, it was thought to be a fibrous growth, attached to the abdominal wall on a previously ventro-suspended uterus.

At operation, the fundus of the uterus was found attached to the abdominal wall. The tumor, 8 cm. in diameter, was situated to the right of the midline, and extended down to the right side of the uterus. It was solid, with glandular, cystic areas filled with black pigment. Because of its extension into the retroperitoneal tissue, and apparent inoperability, only a piece of tissue 6 cm. in diameter was excised for diagnosis. Figs. 156 and 166.

In the cases of adenomyoma of the abdominal wall it was not possible to trace a direct continuity of uterine endometrium to the adenomyoma. Cullen, however, has shown that in many adenomyomas of the uterus this relationship between the endometrium and the adenomyoma could be demonstrated. In Case 2, the adenomyoma of the tube was adherent to the abdominal wall, and from the similarity of the pathologic picture of the two tumors, one is led to believe that the adenomyoma of the abdominal wall arose from that of the tube. In Case 3, the anatomic relationship to the uterus was established, but their pathologic relationship was not microscopically demonstrated. It is therefore impossible to say definitely that the adenomyoma arose from the uterine endometrium.

#### ADENOMYOMA OF THE SIGMOID

**CASE 4.**—The adenomyoma of the sigmoid occurred in a patient, aged 31, who had been married eleven years and pregnant once. She had had an appendectomy, salpingectomy, and partial oophorectomy performed elsewhere. At that time she was told that she had a tumor of the lower bowel which would become a cancer. She presented herself at the clinic because of this tumor. X-ray of the colon, and a proctosigmoidoscopic examination proved negative.

At operation a tumor mass was found encircling the sigmoid, involving a segment of the bowel 4 cm. in length. The sigmoid and the bladder were adherent to a mass around the uterus. Twelve centimeters of sigmoid were removed as well as "tarry" cysts of both ovaries. (Figs. 170 and 171.)

Since the mass in this case was not removed and its true pathologic condition was not known, only the anatomic relation between the uterus and the sigmoid was established. Leitch, however, reports a similar case of an adenomyoma of the sigmoid, in which this viscus

as attached to the posterior wall of the uterus. Specimens from the uterus and the sigmoid showed the same pathologic picture. The

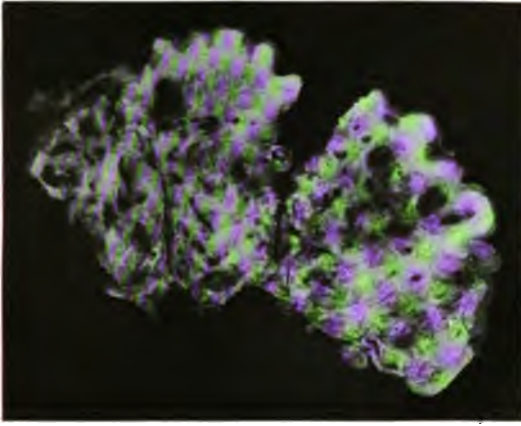


FIG. 157.—(Case 8, 29640.) Adenomyoma of the rectovaginal septum with epithelium intact over tumor mass.

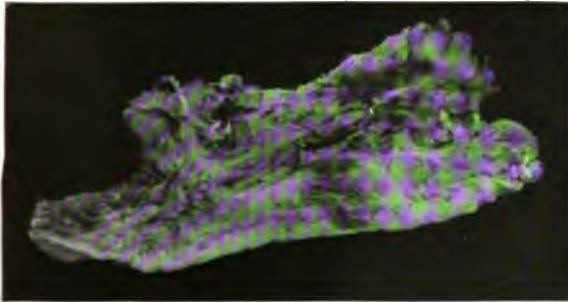


FIG. 158.—(Case 6, 281149.) Adenomyoma of the groin.

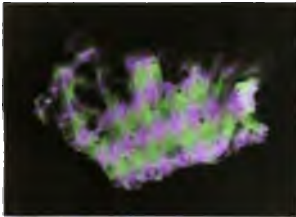


FIG. 159.—(Case 10, 277751.) Adenomyoma of the rectovaginal septum with small cystic areas filled with dark brown pigment.

These facts in these 2 cases lead us to believe that the adenomyoma tissue invaded the sigmoid from the adenomyoma of the uterus. In neither case was the mucosa of the sigmoid involved, thus indicating

that these growths infiltrate from the outer bowel wall and grow between muscle fibers and into the loose connective tissue of the serosa and submucosa.

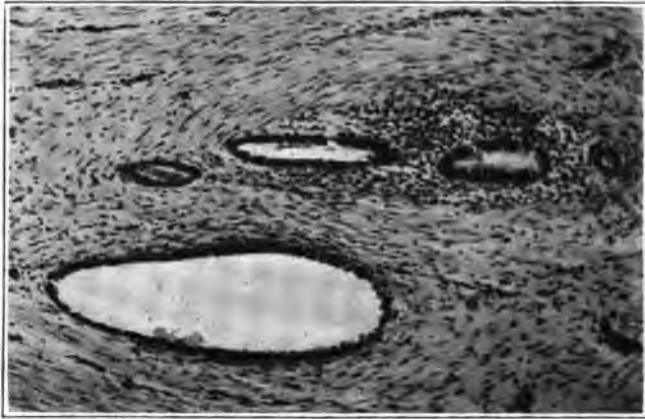


FIG. 160.—(Case 1, 261880.) Adenomyoma of the umbilicus. A group of glands are surrounded by a cellular stroma resembling a typical adenomyoma of the uterus.

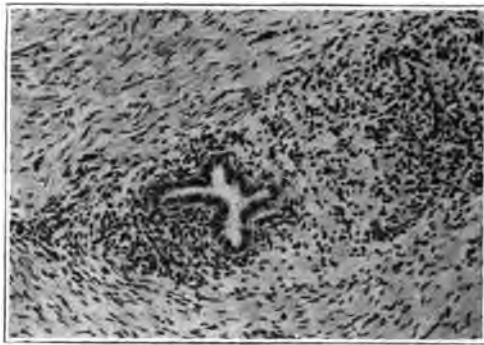


FIG. 161.—(Case 1, 261880.) Same as Fig. 160.

#### ADENOMYOMA OF THE GROIN

Cases 5 and 6 were classified as adenomyoma of the groin, although in Case 6 the tumor was located in the lower right abdomen beneath a scar due to an appendectomy.

**CASE 5.**—This patient who had been married eight years, but had never been pregnant, had come to the clinic five years before because of sterility. At that time her examination was negative, except for several small nodules which were felt behind the uterus. She returned four years later, complaining of a large gland in the right inguinal space which she had noticed only a short time, and which at the time of menstruation became larger and tender.

On examination, a tumor mass was found, fairly hard and tender to touch, presumably a gland, 4 cm. in diameter, in the right inguinal group of lymphatic glands.

The patient returned one year later; the gland had enlarged, and she complained of some pain in the back and lower abdomen. Since nothing further was found on examination than had been noted on former visits, it was decided to excise completely the tumor in the groin. The tumor was diagnosed pathologically adenomyoma (cases 156 to 167).

CASE 6.—This patient, aged 50, single, had had an appendiceal abscess drained twenty-five years before. She complained of a palpable tumor, a right inguinal hernia, and a thickening of the appendiceal scar. Four years before she had noticed in this area two small lumps, slowly increasing in size, which became painful at the time of menstruation.

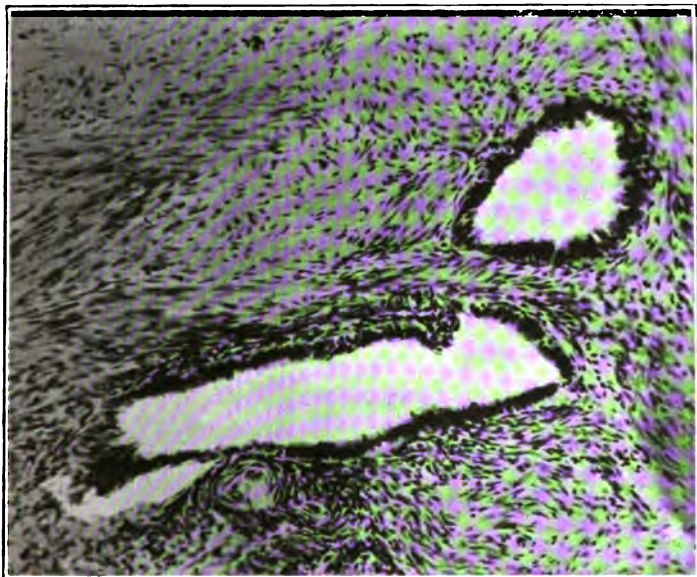


FIG. 162.—(Case 2, 251296.) Adenomyoma of the tube.

On examination, some induration of the appendectomy scar was noticed, as well as a right inguinal hernia and a large pelvic tumor, presumably a fibromyomatous uterus. At operation, the fibromyomatous uterus was removed and the inguinal hernia reduced from within. Later, under local anesthesia, the appendectomy scar was dissected out. The specimen appeared as an indurated mass resembling a keloid, but underneath were cystic areas filled with brown fluid. This tissue, which extended down to the femoral ring, was diagnosed pathologically adenomyoma. (Fig. 158.)

Those adenomyomas of the groin, which have been reported in the literature, were, in most instances, connected with the round ligament.<sup>4</sup> The tumors in our cases showed no relation to this structure, but were situated lateral to it and, at operation, no association could be established, either to the round ligament or any structure closely related to the uterus.



## ADENOMYOMA OF THE RECTOVAGINAL SEPTUM

Cases 7, 8, 9, and 10 of adenomyomas of the rectovaginal septum comprise the entire number observed in the Mayo Clinic during a period of ten years. Since so much has been written concerning such

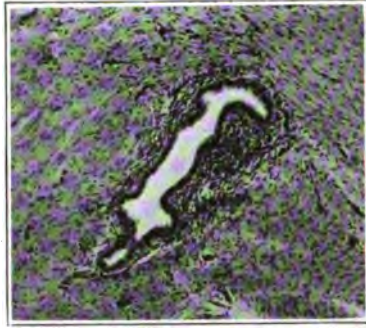


FIG. 163.—(Case 2, 251296.) Adenomyoma of the abdominal wall, showing glandular structures lying in a cellular stroma.

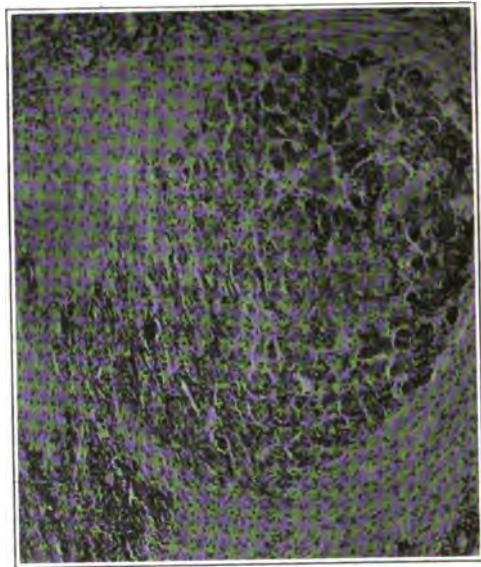


FIG. 164.—(Case 2, 251296.) Adenomyoma of the abdominal wall, showing areas of old hemorrhage around striated muscle fibers.

tumors, we shall not describe our cases in detail, but consider them in a group. The importance of the condition should, however, be emphasized.

CASES 6 TO 10.—The average age of these patients was 37, ranging from 33 to 45. Two patients were married, one of them was sterile, the other had been pregnant three times. Menstruation in each was regular with no intermenstrual bleeding. Two had had previous gynecologic operations elsewhere, one a myomectomy and a ventral suspension, and one a vaginal hysterectomy for hemorrhage and a cervix suspicious of malignancy.

One patient only came for examination because of symptoms traceable to the tumor, which were pain in the rectum at the time of menstruation and difficulty in defecation. In all the other cases the adenomyomas of the rectovaginal septum were found in the course of routine physical examination; all showed a tumor situated in the rectovaginal septum, varying in size from 0.5 cm. to 3 cm. in diameter. In no case was there involvement of the rectal or vaginal mucosa. Only one had a polypoid tumor formation raising the vaginal mucous membrane on the posterior vaginal wall. The diagnosis of adenomyoma was not made clinically in any case.

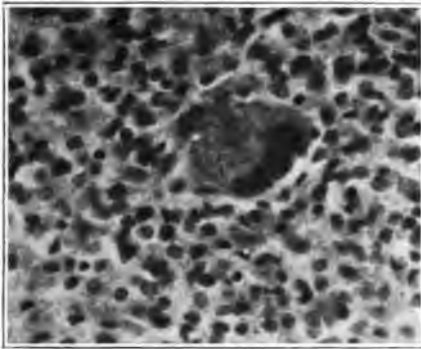


FIG. 165.—(Case 2, 251296.) A foreign body giant cell absorbing old hemorrhage, surrounded by endothelial cells containing old blood pigment.

The postoperative results are of interest, in that the patient with definite symptoms from the tumor complained, three years later, of a pain in the vagina associated with a greenish-yellow discharge. This patient had been treated with radium with questionable results. The other patients have no subsequent history of note. (Figs. 157, 159, 169, 172, 173 and 174.)

Pathologically, extrauterine adenomyomas are identical in appearance regardless of where they are found. They differ grossly from adenomyoma of the uterus, in that the cystic areas are larger and the contents darker brown. (Figs. 153 to 159.) Grossly, the tumors are solid, fibrous, and of a light gray color. Here and there, white bands extend into the tumor substance, while between these bands are areas, dark brown to almost black, varying in size from the head of a pin to cystic areas 1 cm. or more in diameter. On pressure, a dark brown fluid exudes from the larger cystic areas.

Microscopically, the stroma consists of fibrous connective tissue and smooth muscle fibers, the latter in varying amounts. Within

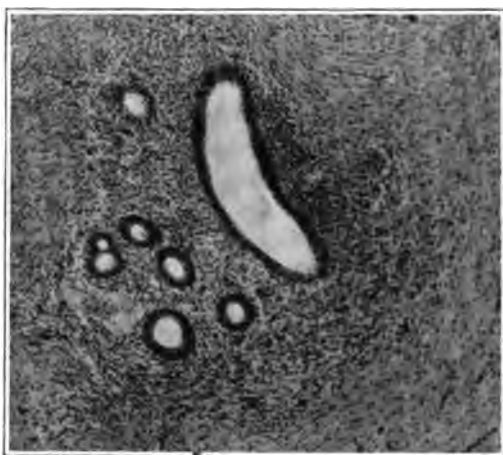


FIG. 166.—(Case 3, 177844.) Adenomyoma of abdominal wall.

the stroma are gland spaces lined with cylindrical epithelium. Some glands are surrounded by a very cellular stroma, the cells of which are regular with round or oval nuclei resting in a very fine reticulum, while

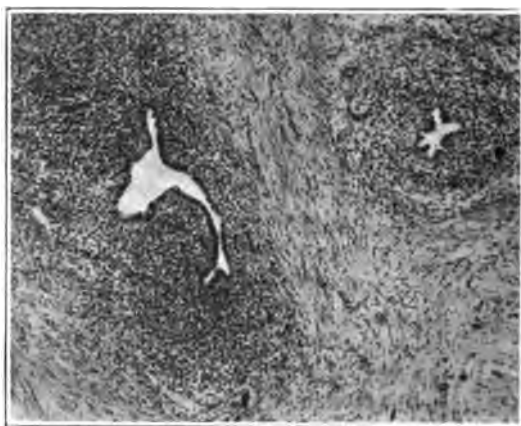


FIG. 167.—(Case 5, 109474.) Adenomyoma of the groin. Note typical uterine gland surrounded by cellular stroma as seen in uterine endometrium.

other glands are immediately surrounded by smooth muscle or connective tissue. In some portions of the tumor substance there is marked evidence of recent and old hemorrhage. In the latter areas

are clumps of endothelial cells filled with old blood pigment and in one of these areas a typical foreign body giant cell is seen enclosing a mass

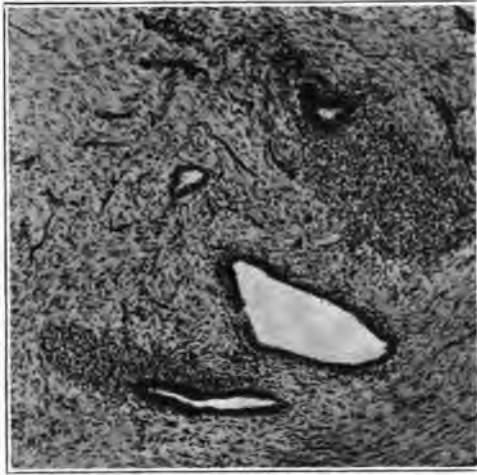


FIG. 168.—(Case 6, 281149.) Adenomyoma of the groin.



FIG. 169.—(Case 7, 144034.) Adenomyoma of the rectovaginal septum, showing glands surrounded by smooth muscle.

of blood pigment. The adenomatous portions of these tumors with their cellular stroma are identical with uterine endometrium. (Figs, 160 to 174.)

Clinically, these tumors give no consistent group of symptoms on

which an accurate diagnosis can be made. However, their location and their slow growth, extending over a period of years, suggest benign tumors. Further, the occasional relation to the time of menstruation, of pain or swelling of the tumor, or less frequently a bloody discharge, should be very suggestive of adenomyoma.

Surgically, adenomyomas, regardless of their remarkable infiltrative characteristics, should be distinguished from malignancy. Especially is this true of tumors in the pelvis, adherent to the sigmoid or

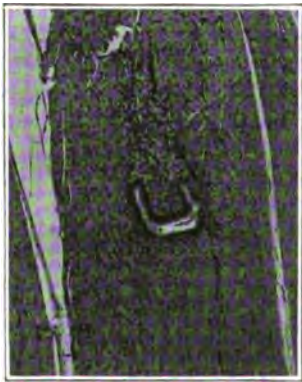


FIG. 170.

FIG. 170.—(Case 4, 250372.) Adenomyoma of the sigmoid.

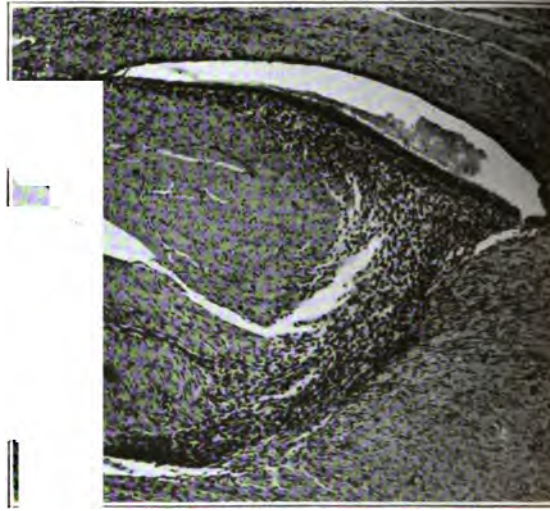


FIG. 171.

FIG. 171.—(Case 4, 250372.) Adenomyoma of the sigmoid, showing cellular stroma invading muscle fibers. Note old blood and serum in lumen of the gland.

the abdominal wall or other structures. Adenomyomas may be recognized grossly in most cases by the fibrous stroma which contains cystic areas filled with a bloody, dark brown, or serous fluid.

The pathologist should distinguish adenomyoma from carcinoma by the regularity of gland structure with normal differentiated epithelial cells without mitoses, and, in most tumors, by the characteristic stroma surrounding the glands. He should also recognize that they are benign tumors, that they grow by invasion, and do not metastasize.

It is also of interest that in our series of cases the true nature of the growth was not suspected before operation. Two were diagnosed malignant, one questionably malignant, and the others were left to be diagnosed pathologically at the time of operation.

All cases occurred in patients between the ages of 29 and 50. Pregnancy apparently had no influence, for 6 of the cases occurred in nulliparous women.



FIG. 172.—(Case 10, 277751.) Adenomyoma of the rectovaginal septum.



FIG. 173.—(Case 9, 101953.) Adenomyoma of the rectovaginal septum.



FIG. 174.—(Case 8, 29640.) Adenomyoma of the rectovaginal septum, showing a small cavity surrounded by a cellular stroma containing small glands.

Of the 10 patients, 6 gave a history of symptoms directly referable to the tumor. One stated that a tumor mass was found during operation, elsewhere, for other symptoms of which the patient complained at that time. The remaining 3 patients had adenomyomas of the rectovaginal septum which were so small that they were giving no

trouble. In these cases, the symptoms, when they were noted in the history, were enlargement, pain in the rectum or vagina at the time of menstruation, or a vaginal discharge.

Our knowledge of the origin of these tumors at present is only theoretical. von Recklinghausen thought they arose from the Wolffian body or duct. Ivanoff, and later Aschoff, according to Lockyer, suggested their origin from the epithelium of the peritoneum of the different regions in which these tumors are found. Cullen believes that they develop from remnants of Müller's ducts or misplaced uterine endometrium. No doubt more extensive work on the embryology of the genito-urinary tract will solve this interesting problem.

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## MALIGNANT MYOMAS AND RELATED TUMORS OF THE UTERUS

(Report of Seventy-two Cases Occurring in a Series of 4000 Operations for Uterine Fibromyomas)\*

NEWTON EVANS

Malignant tumors of the uterus comprise a numerically important portion of the malignant tumors in women. In the registration area of the United States in 1916 the malignant tumors of the uterus caused 23.4 per cent of all deaths from cancer in women<sup>19</sup>. The larger number of the uterine cancers are, of course, epithelial cancers. Zacherl states that the proportion of non-epithelial malignant tumors of the uterus to carcinomas is 1 to 40 or 50. The records of the Mayo Clinic for the period of 1910 to 1918 show 22 borderline and malignant non-epithelial tumors of the uterus, while during the same period there were 873 cases of carcinoma of the uterus, a proportion of 1 to 40.

Notwithstanding this numerical disproportion there is in the aggregate a large number of malignant non-epithelial tumors encountered and reported. These, however, have received much less study than carcinomas of the uterus, and their pathology is poorly understood as compared with that of many other types of malignancy.

The literature is somewhat extensive, beginning with the writings of Virchow in 1860, and followed by papers by Ritter, 1887, Williams, 1894, Pick, 1895, Gessner, 1899, Weir, 1901, Jacobi and Wollstein, 1902, and others, who reviewed the principal features of the subject at various periods. I shall not undertake to review this literature, since excellent résumés have recently been written by Maroney, Geist, Proper and Simpson, and others. Kelly and Cullen in their book *Myomata of the Uterus* (1909) present a very interesting and instructive discussion of the subject with a detailed description of a large series of cases.

\* Work done as a Volunteer Student in Surgical Pathology, under the direction of Dr. W. C. MacCarty, Mayo Foundation, April 16, 1919, to August 15, 1919.

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Two questions with regard to the pathology of this group of tumors apparently have assumed great importance, namely: What is the histogenesis of malignant non-epithelial tumors of the uterus? Do they originate in pre-existing fibroids? Most observers have concluded with regard to the first question that practically all spindle cell tumors arising in the musculature of the uterus originate from smooth muscle cells and tend to differentiate into that type of cell. The most potent factors in helping to arrive at this conclusion have been the modern methods of studying and of differentiating the tissue cell types and, particularly, the application of the differential tissue stains of Mallory. The second question seems also to have been satisfactorily settled by the work of various observers who have demonstrated the existence of malignant myomas and cellular myomas within the structure of fibromyomas, other portions of which were of the ordinary benign tissue type. Williams, in 1894, gave this point careful study. The exhaustive work of Kelly and Cullen on their rather large series of cases also makes it plain that these tumors frequently originate within the structure of fibroids. The present observations lead to the conclusion that this insular transformation of otherwise benign fibroids is not usual, for it was not definitely evident in any of the large series of cases studied. It seems, therefore, that the tumor originates in the uterine musculature, and the structure remains unchanged, or that there is a gradual diffuse transformation in structure which leads to the formation found at the time of removal. This question in reality, however, is of academic interest only. The really important point is that these tumors appear as tumors, or within tumors which, clinically, and sometimes at operation, cannot be distinguished from ordinary fibromyomas except in the very advanced stages of growth, when the extensive local infiltration and fixation of the tumor makes it suspicious, or recognizable as definitely malignant.

From a review of the literature in this field it is evident that there is a serious lack of understanding and agreement as to the histologic criteria which should govern the diagnosis of malignancy in this class of uterine tumors.

Kelly and Cullen found 17 cases among 1400 of uterine fibromyomas which they were willing definitely to denominate "sarcoma"; but in the same series there were 17 other tumors which they looked on as suggestive or suspicious of being sarcomatous.

Miller refers to the cases of Warnekross, who reported the surgical treatment of 7 cases of malignant myoma. Photographs of the tissues of these tumors were submitted to Aschoff who gave it as his unqualified opinion that in only 2 cases of the 7 could the tumors be classified as malignant.



FIG. 175.

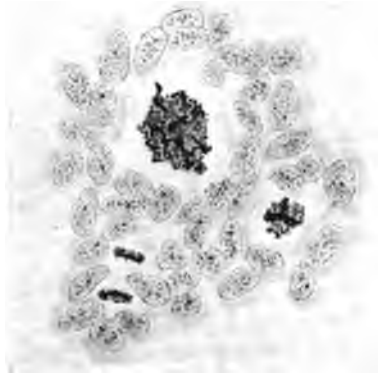


FIG. 176.

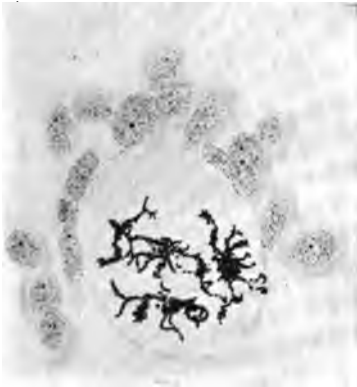


FIG. 177.



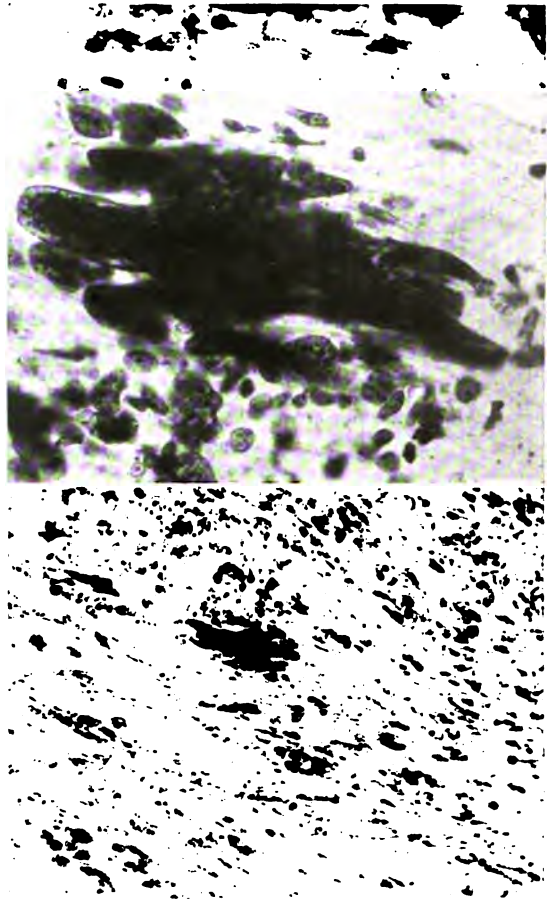
FIG. 178.

FIGS. 175, 176, 177 and 178. Case 3 (125614). (Mitoses 7,600 in 1 c. mm.) Drawings of very large and atypical mitotic figures. Fig. 175 shows a very unusual form with four symmetrical rosettes.

In some of the numerous collected series of cases of uterine fibromyomas the relative proportion which shows malignant change is given as low as 0.4 per cent; in others it is as high as 10 per cent.

Maroney states that the diagnosis "must be a matter of individual interpretation in suspicious cases."

In view of this evident lack of knowledge and lack of acceptance of uniform standards of malignancy as well as degrees of malignancy in this class of tumors, the principal purpose of this study is to make

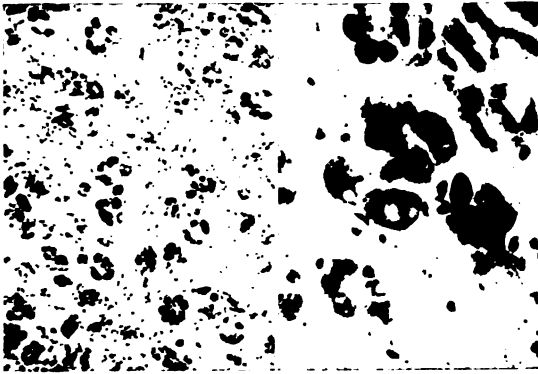


FIGS. 179 (above) and 180. Case 29 (229935). (No mitoses.) Photomicrographs at high and low power, showing structure of a giant-cell tumor, with one giant cell of immense size. Note the size of the immense irregular nucleus with some of the surrounding nuclei of tumor cells of ordinary size, and the relatively large amount of fibrous stroma. Tumors of this type did not recur after removal ( $\times 100$  and  $\times 500$ ).

such comparisons of the histologic findings and the clinical histories of the material available as will serve to contribute something to the establishment of microscopic criteria.

A composite picture of these characteristics, as presented in the writings of several authorities, includes the following points:

1. Increase in size of tumor cells, as compared with normal muscle or benign muscle tumor cells.
2. Shorter and plumper cells with nuclei more nearly oval than normal muscle or benign muscle tumor cells, rounded, and "vesicular" nuclei.
3. Inequality in size and irregularity in shape and arrangement of the cells.
4. Lack of "differentiation" of cells.
5. Unequal staining of nuclei, and deeply staining nuclei.



FIGS. 181 (at left) and 182.—Case 33 (248318). (No mitoses). Giant-cell tumor, with very large nuclei arranged peripherally in the giant cells. Much fibrous stroma. Large nuclei contain vacuoles ( $\times 100$  and  $\times 500$ ).

6. Presence of immense cells (protoplasmic plaques) with hyperchromatic, single, or multiple nuclei (giant cells).
7. Presence of mitotic figures, typical and atypical.
8. Decrease or absence of stroma fibers between the cells.
9. Thinness or absence of vessel walls.

Kelly and Cullen in the descriptions of their 17 positive cases of malignant tumors appear, from a histologic standpoint, to place definite dependence on inequality in size and increase in the size of the tumor cells. And it is evident that they do not look on the presence of mitotic figures or of numerous mitoses as essential to the diagnosis of malignancy in these tumors. In 6 of the cases "nuclear figures" are noted, in 9 no mention is made of their presence, and in 2 it is stated specifically that they were not seen.

Ewing, in discussing the relative malignancy of the different malignant myomas, says that the round-cell and the giant-cell structures are the most malignant.

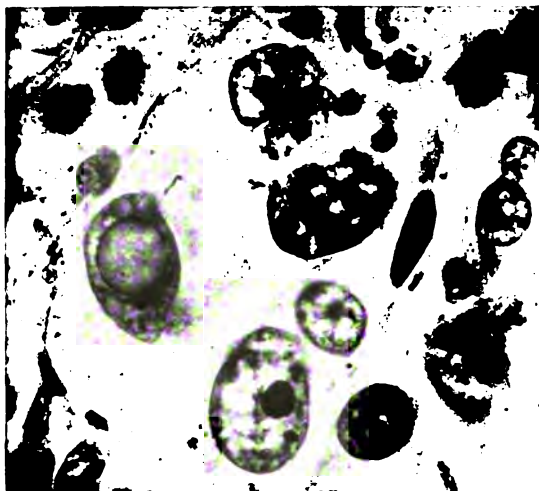


FIG. 183.—Case 2 (77121). (Mitoses 2,400 in 1 c.mm.) Cells of immense size in a very malignant tumor. Very large dense nucleoli and nuclear vacuolation ( $\times 500$ ).

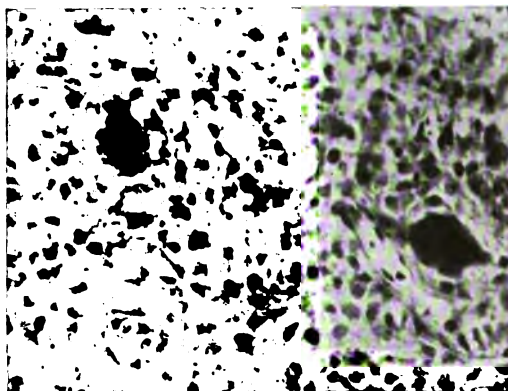


FIG. 184.—Case 7 (64888). (Mitoses 2,560 in 1 c.mm.) Foreign body giant cell in a tumor with much fibrous stroma in its structure, but a highly malignant tumor ( $\times 240$ ).

Proper and Simpson, of the New York State Cancer Laboratory in their recent article, *Malignant Leiomyomata*, present an extremely valuable study of the microscopic characteristics of these tumors since it is based on the correlation of the postoperative course of the

patients with the microscopic structure of the tumors. They divide the tumors into three types varying in the degrees of malignancy which possibly represent stages of malignancy. With reference to their structure they state that "histologically the tumors may vary from those made up of cells of uniform size resembling those which make up leiomyomata, but being somewhat shorter and plumper, with here and there a mitotic figure, up to tumors comprised of cells which are extremely irregular in size and shape, some being masses of protoplasm with giant or multiple nuclei, and showing all varieties of atypical mitotic figures." This statement seems to mean that the presence of the large irregular nuclei and giant cells is in direct proportion to the degree of malignancy and is an important accompaniment of the malignant process. This is in apparent accord with Ewing's statement. Proper and Simpson also make the very important observation that in doubtful cases they depend on the absence of mitotic figures as the criterion of a benign tumor. Mallory believes that the presence of mitotic figures in these myomas is a definite indication that they are capable of infiltration and are, therefore, malignant. Lockyer, in his interesting volume on fibroids, recently published, says that malignant myomas are often difficult to distinguish and emphasizes the tendency to infiltrate and the presence of mitotic figures as a distinguishing characteristic.

The literature contains frequent accounts of metastasis by way of the blood stream of myomas which are said to have the structure of benign or ordinary fibromyomas. Lockyer refers to cases of this kind. Ewing states that so far as he has been able to learn no case has been fully studied in which definite variations from the usual structure were wanting, although in several instances these variations were not very pronounced. Strong is quoted by Maroney as making the very radical statement relative to the existence of microscopic criteria for malignancy in these tumors, that the "only criterion is infiltration and destructive growth. Mere richness in cells, mitoses, and even irregularities in size of cell do not constitute sarcoma." Strong further states: "There never can be any absolute criterion for their malignancy and their interpretation will always be affected by the personal equation of the individual observer." Ewing, sharing the uncertainty of practically all observers relative to the microscopic diagnosis, says: "Sarcomatous tendencies and precancerous changes do not constitute real sarcoma or cancer." It is thus evident that

many "very cellular" tumors or myomas exist which give difficulty in classification as far as their real malignancy is concerned and which are sometimes classified by the pathologist as malignant, and sometimes as benign or doubtful.

*Mitotic figures.*—From the foregoing statements and other observations it may be assumed that, in a general way, the presence in the tumor tissue of evidences of indirect cell division is looked on as a characteristic of the malignant growths of the types under consideration. So far as I can learn, however, no attention has been given to a determination, in a given case, of the actual or relative numbers of mitotic figures as related to the degree of malignancy of the tumor, or whether or not any such relation exists. The facts presented in the present series of cases show that such relationship undoubtedly does exist.



FIG. 185.—Drawing of nuclei of tumor cells showing changes evidently those of direct nuclear division-amitosis. Series showing progressive changes in long, oval nuclei of ordinary size.

The series comprises 72 cases diagnosed as "sarcomatous," "cellular," or "very cellular" fibromyomatous tumors in the Laboratory of Surgical Pathology of the Mayo Clinic in the years from 1906 to 1918 inclusive. All tumors of this kind observed in about 4000 operations for the cure of uterine fibromyomas are included.

Table 1 serves to show the very definite relationship between the more evident characteristics of the cellular structure of the tumors, particularly the presence and relative proportions of the mitotic figures, and the clinical outcome of the disease. In each case evidences of indirect cell division were searched for and careful estimates were made of the actual number of these figures in a given area of the tumor tissue; the numerical values were expressed as the number of mitotic figures seen in 100 microscopic fields of a  $\frac{1}{12}$  oil immersion lens. These values are also translated in an adjoining column into the

number of dividing cells in a cubic millimeter of the tissue, taking into consideration in this estimation the thickness of the tissue section.

The tumors readily divide themselves into three definitely delimited groups, on the basis of the number of mitotic figures present. In the first 13 cases the tumors show from 2200 to 12,000 mitotic figures for each cubic millimeter. Cases 15 to 25 form a group having from 200 to 800 in a cubic millimeter. In the remainder of the cases the tumors either contained no figures on examination or only a very few, one or two being found after long searching. One of the most noticeable features of the tabulation is the definite numerical separation between the first and the second groups, no tumors being found which showed a numerical value between 800 and 2000. It would not be justifiable to conclude that in a larger series of tumors, or in another similar series, values within this hiatus might not be found, yet the numerical distinction is so clear-cut that it cannot escape notice.

The real importance of such distinctions, however, becomes evident when the after-course of these cases is considered. Of the 13 patients in the first group, 11 had recurrences within periods of from one month to eighteen months. Only 2 patients are known to be living; they give no indication of a return of the malignant tumor, seven months and four months respectively, since operation, periods too short to preclude the possibility of later recurrence. However, since the recurrences were rapid in the other cases one is justified in hopeful prognoses in these 2 cases.

In definite contrast to the cases in the first group, in the 11 cases in the second group, having mitotic figures in the proportion of 200

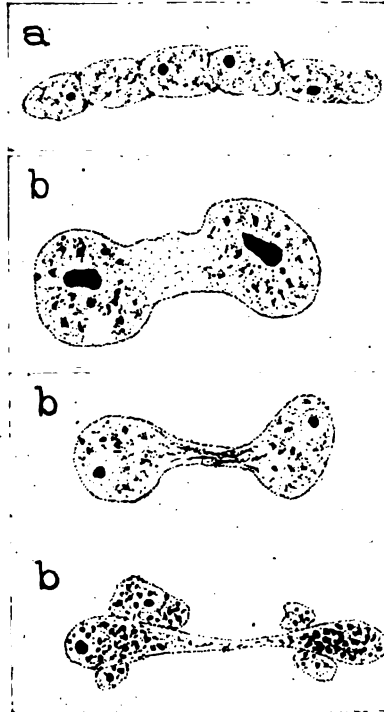


FIG. 186.—Drawing. *a*. Result of multiple change of a long nucleus. *b*. Forms seen in giant cells of tumors having no mitotic figures.



to 800 to each cubic millimeter, there has been no mortality; at least in the cases about which we have been able to obtain a recent report, 9 of the 11, and there are good reasons for believing that the same is true in the other 2 cases.

In the remaining group of 48 cases, in which no mitotic figures are seen, or only a very few, there is no mortality from recurrence, at least in a large majority concerning which it has been possible to obtain recent reports.

This striking evidence of the importance of numerous mitotic figures as an indication of definite malignancy makes it desirable to study the reports of similar series of cases from this viewpoint. The very complete description of the histology and the clinical features of Kelly and Cullen's 17 cases makes an interesting comparison possible. Eleven of their 17 patients survived the operation and so are available for comparison on the basis of after-history. Only 4 of the 11 died of recurrence. In each of these 4, mitotic figures are mentioned as being present, in one "many" were seen, and in one other as many as "six in a field." Of the remaining 7 patients without recurrence, only one tumor is mentioned as showing mitotic figures, and in this there was said to be "one here and there." One might be justified from a study of these descriptions in the opinion that the four fatal recurring tumors belonged in the same group with those of this series having many mitotic figures, and that the one tumor which had mitotic figures "here and there" belonged in the next group having fewer mitoses and clinically showing no recurrences. It might be questioned whether Kelly and Cullen are entirely right in classifying in their group of 17 definitely malignant "myosarcomas" the 9 cases which are not mentioned as showing mitoses, and 2 which are described specifically as not showing such figures. In none of these patients having tumors with no mitoses recorded, who survived operation, was there any recurrence.

A personal communication from Dr. Simpson relative to the series of 22 cases of this type of tumor recently reported by Proper and Simpson indicates that the findings in their specimens, with reference to the relative number of mitotic figures in sections of the tumors of different histologic types, are substantially in harmony with my series.

While we are considering the question of mitosis it would be well to mention the frequent occurrence, in the tumors composed of a mass of very large sized tumor cells, of numerous mitotic figures of unusual

form and gigantic size. The drawings in Figure 175 show several examples, including the unusual figure of a double division resulting in the formation of four newly formed symmetrical rosettes. These large and so-called atypical mitotic figures are unquestionably always a sign of high grade malignancy.

*Giant cells and hyperchromatic nuclei.*—Another histologic feature which demands consideration in a study of these tumors is the presence in a certain proportion of cells with large, irregular, hyperchromatic, and usually multiple nuclei. Some of these are so immense as almost to exceed belief (Figs. 176, 177 and 178). The importance of these changes in the diagnosis of malignancy or degree of malignancy, judging from the statements in the literature of the subject, is usually considered to be very great. A study of Table 1 will give a basis for rather definite conclusions in regard to this point.

It is true that in the first group of 13 cases, including all those of the series in which there was postoperative recurrence, giant cells were present in varying degree, but in a considerable proportion of them in comparatively small numbers. Most of the tumors in the next group of the series (Cases 14 to 24), none of which recurred, that were characterized by a relatively small number of mitotic figures, had no giant cells, and only a few had any giant cells. The phenomenon of greatest interest, however, is that in many of the tumors of the third group (Cases 25 to 72) giant cells were numerous and in a few tumors they were present in such numbers, and of such size and complexity, as to attract attention. It should be remembered that in this group there were no recurrences and histologically the tumors were characterized by the absence of mitotic figures or by the presence of only a very few at the most. A review of the literature indicates that such tumors have usually been looked on as malignant. The facts evident in this series compel the conclusion that there is nothing to indicate that the presence of the giant cells alone is an indication of a high degree of malignancy or indeed of malignancy at all. In the tumors showing the greatest tendency to giant-cell formation, but without mitotic figures, it is invariably found that the cells are not closely packed but are separated by large amounts of fibrous stroma with a tendency to hyalinization. Kelly and Cullen believe that the frequent association of this type of cell and stroma indicates malignancy and that the presence of the hyalinization is an important factor in its pathogenesis. It may be concluded that these cellular

changes are a phenomenon of degeneration coincident with fibrosis and hyalinization rather than a manifestation of the exaggerated productive and reactive phenomena which characterize true malignant tumors. The origin of the cells which take on this unusual type of change is somewhat uncertain, but from the cellular relations it seems that many of these very large mononucleated and multinucleated cells are modified muscle cells while others, from their position in relation to minute vascular channels, appear to originate from endothelial cells.



FIG. 187.—Case 61 (248302). (No mitoses.) Photomicrograph showing numerous long oval nuclei in direct division ( $\times 1000$ ).

The morphology of these giant cells is distinctly different from that of the so-called foreign body giant cells which are found in many tumors, in the lesions of the infectious granulomas, and in the vicinity of various foreign bodies in the tissues. Those appearing in the tumors in our series should be classed as true tumor giant cells. In a few of the tumors studied, however, there is a tendency to the formation of the foreign body giant cells. This tendency is marked in only one of the tumors (Case 7, Fig. 179). In these figures numbers of giant cells of this type are scattered throughout various portions. They are characterized by a compact densely acidophilic staining cytoplasm with numerous small oval or round nuclei centrally located. These cells probably have their origin in modified connective tissue stroma

cells or in some type of wandering cell. In contrast with these cells are the characteristic tumor giant cells which have irregularly shaped, lightly staining, indistinct bodies with very large, unequally sized, irregularly shaped, deeply staining nuclei, usually arranged in a ring at the periphery of the cell body. Many of these nuclei have very large densely staining chromatin granules, and often the chromatin is disposed in threads (Fig. 176). In many of the sections of the very malignant tumors many very large cells are found undergoing unusual forms of mitosis. But typical multinucleated giant cells with nuclei in the stages of mitosis have not been found. This leads to the conclusion that the true tumor multinucleated giant cell forms by the direct, or amitotic, division of the nucleus. Such dividing nuclei are in fact frequently seen.

*Direct cell division of tumor cells.*—Throughout the tissue of a large proportion of these uterine tumors are seen nuclear forms, the morphology of which can be interpreted only as that of cell division by the direct or amitotic method. This is particularly true of those tumors which do not belong to the more malignant type, containing no mitotic figures, and the growth of which cannot be accounted for by mitotic cell division. The drawings and the photographs of nuclei thus dividing will give a general impression of the phenomena as seen in the sections. There are two distinct forms of such nuclear division. One of these is seen in the large nuclei of the large hyperchromatic giant cells described in the preceding paragraph. These nuclei may divide equally, but more often they divide unequally by a process of lengthening and constriction at the middle; the two portions are pulled apart, a large strand of nuclear material connecting them, thus assuming a distinct dumb-bell shape (Fig. 180). The other form of direct nuclear division is seen in the tumor cells of ordinary size, of long or short oval shape, or with rounded nuclei. The cleavage is usually preceded by a distinct indentation on one side of the nucleus before it is separated into two equal parts. The line of cleavage is in a distinctly oblique direction, the degrees of obliquity being greater in the shorter and plumper nuclei (Fig. 181). Occasionally nuclei of great length will be seen, evidently dividing almost simultaneously by a multiple cleavage so that a chain of attached oval nuclei results (Fig. 180).

The conclusion is apparently justified that the direct cellular division observed accounts for the tumor growth in the growing

tumors which show no signs of growth by mitosis. The subject of amitotic cell division is discussed at some length by Wilson in his book on the cell. He emphasizes three points of special interest in this connection:

1. Cells undergoing amitotic division have a tendency to become larger in size than other cells of the same tissue type.
2. The cells have a tendency to nuclear division without division of the cytoplasm, thus producing multinucleated giant cells. Both of these tendencies are very definitely illustrated in the large nuclei

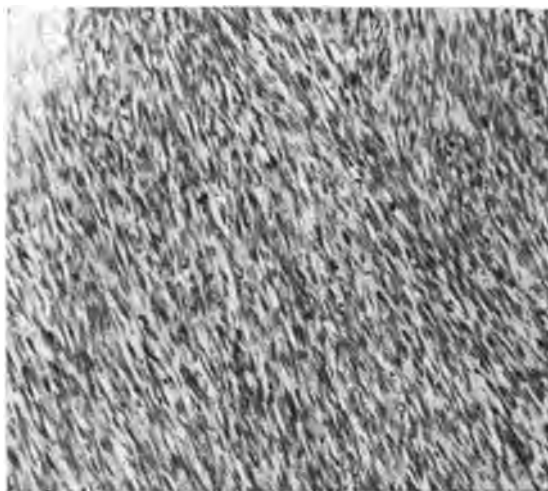


FIG. 188.—Case 8 (38352). (Mitoses 4,000 in 1 c.mm.) Marked degree of polarity and alignment of the most malignant tumor as compared with the irregular arrangement of the cells in the less malignant tumor.

of the tumor giant cells which so frequently characterize these tumors and especially those not showing definitely malignant tendencies.

3. Direct cell division is an indication of degeneracy of the cells involved.

On this last point Wilson quotes von Rath: "When once a cell has undergone amitotic division it has received its death warrant; it may indeed continue for a time to divide by amitosis, but invariably perishes in the end." Wilson states, however, that this is probably an extreme view as there are definite examples to the contrary in lower forms of life. It may be assumed, therefore, that the direct nuclear division which was so frequently seen in the tumors of this series undergoing fibrosis and hyalinization as well as the marked tendency

to giant-cell formation under the same conditions is a manifestation of biologically regressive cellular changes.

Kimura has recently reported an interesting and important piece of work which throws additional light on the problem of the relation of mitotic figures (or evidence of frequent indirect cell division) to malignancy. The purpose of his experiments is to show the influence of the x-ray on the growth and invasive power of malignant tumor tissue, using susceptible animals (mice) and artificial tissue cultures in parallel series. An appropriate dosage of x-ray rendered the cancer

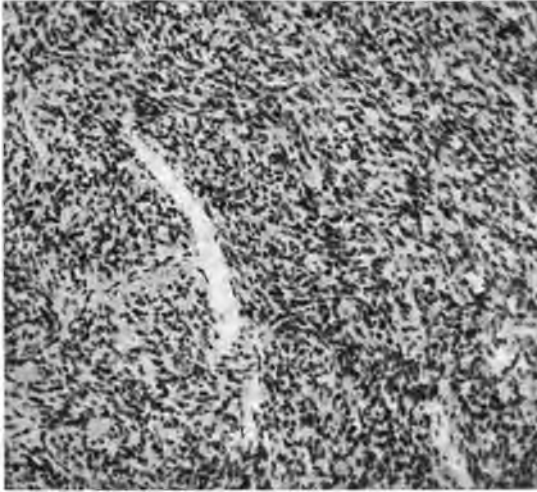


FIG. 189.—Case 27 (215251). (No mitoses.) See Figure 188.

tissue incapable of invading the susceptible animals but the artificial cultures of the irradiated cancer tissue grew just as freely as the control tissue cultures. The remarkable fact was noticed that the tissue exposed to the x-ray grew in artificial culture without any mitotic figures while the control tissue grew with large numbers of mitotic figures. The type of cell division concerned in the growth of the tissue which had lost its invasive power in animals must have been the direct or amitotic type. It seems that the process of mitotic cell division had some relation to the malignancy of the tumors and that with the loss of their mitotic figures they lost their invasive powers. These interesting results are in harmony with the facts observed in the group of malignant uterine tumors in this series since only those tumors which contained large numbers of mitotic figures were able so successfully to invade the tissue as to recur after removal.

*Tumor cell differentiation.*—While it is true that in many of the more malignant of these tumors there is a decided decrease in those characteristics which are considered as signs of differentiation, in practically all a greater or lesser degree of spindle shape, polarity, and alignment of the tumor cells are recognizable. In some of the most malignant this is very pronounced, much more so than in many of the cellular tumors which evidently have little if any real malignancy.

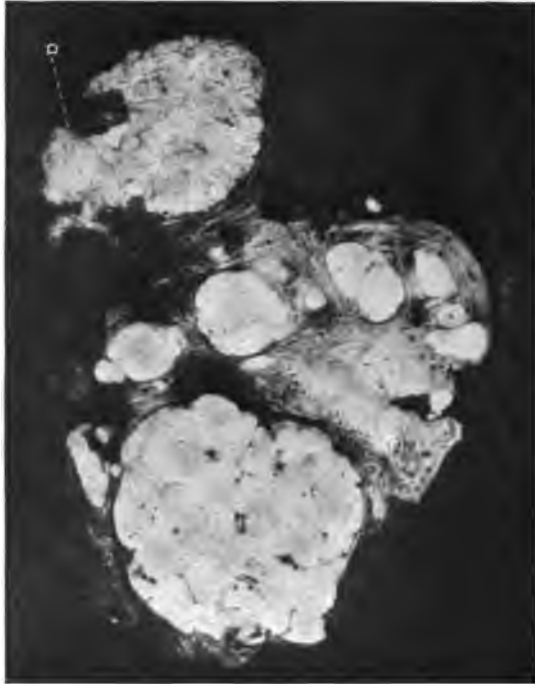


FIG. 190.—Case 43 (76296). (Very few mitoses.) Gross appearance of section through a fixed specimen of uterus containing multiple fibromyomas. One of the tumors, *a*, is very cellular. Its yellow color is indicated by the darker shade in the photograph. It contains an area of hemorrhage.

nancy. This may be easily seen by comparing the appearance of the sections in Figure 182. Therefore, it is evident that the presence or absence of these characteristics is not an essential criterion.

The one dependable microscopic feature so far considered is clearly that of abundant mitotic figures in the extremely malignant cases. The question of the existence of other constant criteria should be considered. It seems to me that the most important microscopic features aside from the frequency of mitoses are:

1. The large size of the great mass of the tumor cells in a given case, and a marked inequality in their size. In those very malignant tumors which are characterized by this type of cellular structure many abnormally large mitotic figures are apparently invariably found (Fig. 175), and such figures otherwise unusual in their morphology.

2. The relative decrease in the amount of fibrous stroma.

3. The growth among the tumor cells of blood vessels with very thin walls or with walls entirely wanting.

4. The relative increase in the size of the nucleus of the tumor cells as compared with the mass of the cytoplasm of the cell body.

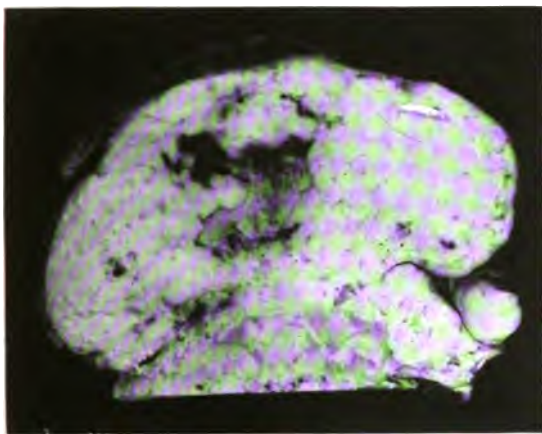


FIG. 191.—Case 11 (213999). (Mitoses 12,000 in 1 c.mm.) Natural size of a section through the fixed specimen. The smooth appearance of the cut surface is evident in contrast to the fibrous appearance of the ordinary fibroid.

While all these changes are important, careful study of the material shows that none is constant, that is, invariably present in the very malignant tumors, and always absent in those not malignant. Notwithstanding this fact, it is well to note that the tumors composed of a mass of closely packed cells of very large size are invariably extremely malignant, although it is not true that all the malignant tumors have this particular morphology.

It would be rash to maintain that other constant, easily recognizable microscopic criteria of this particular type of malignancy do not exist; but up to the present time I have not been able to recognize any single criterion which is constant aside from the peculiarities in mitoses, although the presence of several of the prominent characteris-



tics when occurring in combination may possibly be sufficient to insure the accuracy of the diagnosis of malignancy without giving any attention to the question of mitotic figures.

*Frequency of occurrence.*—Reference to the literature indicates that frequently efforts have been made to estimate the incidence of the malignant non-epithelial tumors of the uterus with the total number of cases of uterine fibroids. Table 2 gives an idea of some of the results. The wide variation of these estimates is no doubt largely due to the absence of uniform standards rather than to actual variation in the incidence of the malignant tumors.

The 72 patients in the present series, in which the cellular and definitely malignant tumors are included, were examined in the Mayo Clinic during the years 1906 to 1918 and three months of the year 1919, during which time operation was done in approximately 4000 cases of uterine fibroids. However, in order to obtain relative figures which will have much value as an indication of the real incidence of these tumors of varying degrees of malignancy, it will be necessary to make the comparison from material collected over somewhat shorter periods, since only during the past few years has sufficiently painstaking investigation been made of all the fibroids which are removed at operation to insure the recognition of practically all the unusual myomas, particularly those of the lesser degrees of malignancy. Among the 968 cases of operation for removal of fibromyomas during the two years 1917 and 1918 were 6 cases of the most malignant type, those tumors containing from 2200 to 12,000 mitotic figures to the cubic millimeter. When the tumors having from 200 to 800 mitotic figures to the cubic millimeter are included there are 12 in all; and including all these with the remainder of the series, that is, those having the cellular structure but lacking the frequent mitoses, gives 38 in all. The percentage for the first group was 0.62, for the first and second groups together 1.25, for the three groups 4.00

During the period from 1910 to 1918 inclusive the total number of fibroid operations was 3297; only 13 cases (0.39 per cent) belonged to the very malignant group; adding the 9 cases of the second group, there are 22 cases (0.67 per cent). The figures for the third group of this longer period are too inexact to be included. When the figures for the two year period and those for the nine year period are compared the percentages for the shorter period are found to be definitely larger;

and it is probably safe to conclude that these larger percentages more nearly represent true conditions.

A comparison of the percentages for the two year period with the figures taken from those of other observers, as shown in Table 2, leads one to believe that in a rough way those series which give percentages less than 1 per cent are made up of only the most malignant tumors, those in Group 1. This would include such groups of cases as Broun's 1500 cases at the Woman's Hospital, New York, and the 337 cases of Noble. Those series giving percentages between 1 and 2 are probably made up largely of cases that would be included in our Groups 1 and 2. The higher figures are no doubt in series which include not only the more malignant types but also practically all the cellular tumors, the majority of which manifestly show little malignancy clinically and, as we have shown, contain few or no mitotic figures.

*Degrees of malignancy and relation of the different types of tumors.*—Three questions remain to be considered. (1) The degree of malignancy of the tumors which are classified outside the group of manifestly malignant tumors, but including tumors none of which recurred after removal (Groups 2 and 3). (2) The question of the biologic relationship between these less malignant tumors and the most malignant ones. Are they a fixed type of tumor, or are they simply in a stage of metamorphosis, representing a transition stage between the ordinary fibroid with its mature, fully differentiated type of cell and the real cancer? (3) Is it not possible that these very cellular myomas with short spindle cells and short plump nuclei and an occasional mitotic figure are simply ordinary fibromyomas in an actively growing phase, and at a later period may they not cease their active growth and become ordinary fibroids with the structure that the majority of fibroids possess? With regard to the last of these questions it seems possible that there may be a stage of growth in which the balance may turn in either direction; on the one hand, back to the fully differentiated type and, on the other, to a still more active tumor growth in which the cells vary more widely from the adult type and in which the increased rate of growth and increased power to invade tissue is indicated by an increased number of mitotic figures.

With regard to the first two of these questions the positive opinion seems justifiable, although not proved, that the actively growing tumors which contain an appreciable number of mitotic figures are

in a stage of transition toward actual malignancy and, if undisturbed, will become malignant.

A tentative classification of the tumors of this series, exclusive of those in the first group, those definitely malignant, is as follows: Group 2 includes those with a mitotic figure content of from 200 to 800 to the cubic millimeter and should be looked on as in a transition stage, borderline tumors between the definite malignant group and the remaining group of cellular tumors. The cases in Group 3 are premalignant and as such presumably have malignant tendencies.

*Gross characteristics.*—These uterine tumors appearing in the locations of, and in form and general appearance resembling fibromyomas, have a color and consistency which as a rule are characteristic; and it should be remembered that they occur frequently in the uterine ligaments and other locations where fibromyomas are found. The color is difficult to describe but is remembered when once seen and recognized. It may be said to be a shade including pink, yellow, and gray. Fixed gross specimens have a yellowish tinge, which distinguishes them from the ordinary fibroid. The tissue is much softer and has a smooth homogeneous cut surface as compared with the firm fibrous surface of the usual fibroid, and it is decidedly more friable. In the definitely malignant forms the tumor mass is still more friable and varies in color, due to hemorrhage and degenerative and necrotic changes. In most of the tumors of the definitely malignant type the infiltration and destruction of the uterine and other pelvic structures involved is evident, but the less malignant forms are usually as definitely delimited from the surrounding myometrium as is the ordinary fibroid.

*Metastasis.*—Definite indications of metastasis to distant organs were not found in any of these cases. From the findings at operation and from the subsequent histories of the fatal cases there was evidence of extensive local and abdominal metastasis.

*Clinical characteristics.*—The striking feature of the preoperative history is its resemblance to the history of the ordinary fibroid case and the entire absence of any points in the history or physical examination which make it possible to suspect malignancy except in those cases in which the extension is so far advanced as to make operative cure or any other cure impossible.

In the first group 2 patients only were living without recurrence, one seven, and one four months. One of these patients had the small-

est tumor of the group, 2 cm. in diameter; it was interstitial in location, without macroscopic evidence of infiltration, and it had the smallest number of mitotic figures of any of the tumors included in the group, 2200 to the cubic millimeter. The other patient reported no signs of recurrence four months subsequent to operation. The tumor in this case was large, subserous, pedunculated, 17 cm. in diameter, and adherent to the omentum. Not including the very small tumor just mentioned there were 2 cases in which the tumors were located interstitially; they showed no definite macroscopic evidence of infiltration beyond the uterine body. Both of these, however, recurred and were fatal.

As compared with other types of malignant tumors nonepithelial uterine tumors are said to be comparatively low grade in malignancy. This seems to be true in so far as metastasis in distant organs is concerned. In the present series definite indication of distant metastasis was not found in any case. But from the standpoint of rapid and extensive infiltration these tumors must be classified as extremely malignant.

A comparison of the ages of the patients in the different groups of the series at the time of operation shows that as a group the patients with very malignant tumors averaged fifty years, while all the others averaged forty and one half years. The patients in Group 2, with the border-line tumors, averaged forty-one years. A rapidly growing tumor at or after menopause is very suggestive of this type of malignancy.

*Treatment.*—Five cases in this series were treated postoperatively with the x-ray and radium, but the after-histories indicate that no cures were accomplished in those cases in which the operative and microscopic examinations indicated extreme malignancy. One case (Case 18) is of special interest in this connection. The tumor microscopically belonged to the group of border-line or transition tumors having 800 mitotic figures to the cubic millimeter; at operation such extensive adhesions were found that the tumor could not be removed. The patient was given prolonged x-ray and radium treatment. After two and one half years she is alive and apparently well with some regression of the tumor.

The present plan of surgically removing all uterine fibroids of appreciable size seems to be the procedure of choice. The low operative mortality figures which are shown by the work of skilled surgeons

in the better hospitals are an argument in favor of the operative method.

In the present series of 72 cases there were no operative deaths. This remarkable absence of fatalities in a group of cases of so serious a nature must be looked on in a degree as accidental as is indicated by the usual operative mortality percentages in operations for fibromyomas.

*Terminology.*—Several different names have been used to designate the malignant non-epithelial tumors of the uterus of the type discussed. Among these may be mentioned "sarcoma," "myosarcoma," "myoma," "sarcomatodes," "leiomyosarcoma," "myoma malignum," "malignant," "leiomyoblastoma," "malignant leiomyoma," and "malignant myoma." In the interest of a uniform terminology it seems well to use the term "malignant myoma."

#### SUMMARY

There is evident need of the establishment and recognition of histologic standards of malignancy in the classification of the non-epithelial uterine tumors.

In the present study the only single constant microscopic evidence of definite malignancy is the presence of large numbers of mitotic figures.

Many of these tumors have numerous large giant cells with multiple hyperchromatic nuclei which are often looked on as evidence of malignancy, but they do not contain mitotic figures. There is no evidence that such tumors are malignant.

In the less malignant tumors not containing numerous mitotic figures there are morphologic evidences of division of tumor cells by direct cell division.

Clinically the majority of patients with definitely malignant tumors present themselves for treatment about the climacteric or later. The tumors are difficult to distinguish in the earlier stages from ordinary fibromyomas, they are not cured by x-ray or radium, and the surgical removal of all fibroids of any appreciable size seems to be the best treatment.

**Note 1.**—The computation to determine the number of mitotic figures in a cubic millimeter of tumor tissue: Diameter of oil immersion

field—0.170 mm., radius 0.085 mm., area of one field—(3.1416 times the square of the radius) 0.022698 sq. mm. Taking the average thickness of section as 0.011 mm., the cubic contents of one microscopic field would be 0.000249678 c. mm., or approximately 0.00025 c. mm., or 14000 of 1 c. mm. Therefore, having determined the number of mitotic figures in 100 fields the number in a cubic millimeter would be 4000 times the average number in one field or 40 times the number in 100 fields.

**Note 2.**—A vaginal myomectomy. At first operation the malignancy was not discovered, but it was discovered at a second operation following recurrence.

**Note 3.**—At first operation a subtotal abdominal hysterectomy was done; the malignancy was not recognized. A second operation was done because of recurrence.

**Note 4.**—In this case the removal of the tumor mass was not accomplished, but was discontinued before completion. A tube was left in the abdominal wound to facilitate radium treatments, of which the patient subsequently had a number; x-ray treatments were also given. The patient was alive at the end of one year.

**Note 5.**—The patient died three and one half months after the hysterectomy from an acute peritonitis, following a cholecystectomy; the death had no relation to the previous condition.

**Note 6.**—Fragments only removed. Tumor regarded as inoperable and not removed.

TABLE 1.—TABULATED FINDINGS IN 72 CASES OF MALIGNANT MYOMAS AND RELATED TUMORS OF THE UTERUS

Case	Mitotic figures (Note 1)		Cells		Giant cells	Opera- tive death	Recurrence	Death after operation	Diagnosis at operation
	In 1/12 micro. field	In c. mm.	Size and shape						
1 (33870)	120/100	2400	2 spindle		Many	No	Yes	4½ mos.	Sarcoma
2 (77121)	60/100	1200	4 round, oval, mixed		Many	No	Yes	7 mos.	Sarcoma?
3 (125614)	190/100	3800	3 spindle, mixed		Few	No	Yes	9 mos.	Sarcoma?
4 (207128)	300/100	6000	3 mixed		Many	No	Yes	6 wks.	Spindle-cell sarcoma.
5 (239225)	175/100	3500	2 round, oval		Many	No	Yes	12 mos.	Mixed cell sarcoma
6 (55911)	55/100	1100	2 spindle		None	No	Yes	.....	Sarcomatous
7 (64888)	84/100	1280	2 spindle, round		Foreign body	No	No 7 mos.	3 mos.	Degeneration and necrobiosis (Note 2)
8 (38352)	100/100	2000	2 oval, mixed		Few	No	Yes	6 wks.	Sarcoma
9 (11435)	129/100	1860	3 round, oval, mixed		Few	No	Yes	1 mo.	Necrobiosis (Note 3)
10 (119219)	141/100	2820	1 spindle, oval		Few	No	Yes	17 mos.	Sarcoma
11 (213833)	55/100	1160	2 oval		Few	No	Yes	2 mos.	Sarcoma
12 (213099)	300/100	6000	2 round, oval		Few	No	Yes	13 mos.	Sarcoma
13 (258090)	120/100	2400	1 mixed		Few	No	Yes	.....	Sarcoma
14 (85951)	14/100	280	2 round, oval		None	No	No 4 mos.	.....	Degeneration. Fibroid.
15 (85977)	5/100	100	2 round, oval		None	No	No 9 yrs.	.....	Myosarcoma. Degeneration
16 (103207)	13/100	260	1 oval		None	No	No 3 yrs.	.....	Sarcomatous fibroid
17 (169450)	10/100	200	2 round, oval		None	No	No 5 mos.	.....	Angiomatous fibroid
18 (176816)	20/100	400	1 round, oval		None	No	No 3 yrs.	.....	Sarcoma (Note 4)
19 (184003)	17/100	340	2 round, oval		None	No	No 1 yr.	.....	Sarcoma
20 (186793)	5/100	100	1 spindle, oval		None	No	No 2½ yrs.	.....	Early myosarcoma
21 (201753)	6/100	120	1 oval		None	No	No 10 mos.	.....	Spindle-cell sarcoma
22 (224262)	6/100	120	1 spindle, oval		None	No	No 10 mos.	.....	Myosarcoma
23 (239181)	20/100	400	2 mixed		Few	No	No 1 yr.	.....	Myosarcoma
24 (1591)	8/100	160	Varied		Many	No	No 3½ yrs.	.....	Sarcoma?
25 (93251)	None	None	1 spindle, oval		Few	No	No 3½ yrs.	.....	Sarcoma?
26 (187068)	Very few	None	2 mixed		Few	No	No 1½ yrs.	.....	Cellular hypertrophy
27 (215251)	None	None	1 mixed		Small areas	No	No 1½ yrs.	.....	Cellular
28 (234819)	Very few	None	1 spindle, oval		Few	No	No 16 mos.	.....	Fairly cellular
29 (239935)	None	None	Varied		Many	No	No 14 mos.	.....	Sarcomatous
30 (338918)	None	None	2 mixed		Few	No	No 1 yr.	.....	Myosarcoma

TABLE 1.—(Continued)

31	(241253)	None	None	2, spindle, oval	Few	No	No 11 mos.	Fairly cellular
32	(242747)	None	None	2, mixed	Few	No	No 11 mos.	Secondary hypertrophy
33	(246318)	None	None	2, mixed	Many	No	No 10 mos.	Malignancy
34	(265765)	None	None	2, round, oval	Small areas	No	No 3 mos.	Fairly cellular
35	(6613)	Very few	...	1, spindle, oval	Few	No	No 11 yrs.	Sarcoma
36	(9105)	Very few	...	2, spindle, oval	Few	No	No 9 yrs.	Sarcomatous degeneration
37	(37931)	None	None	1, spindle, oval	Few	No	No 8 yrs.	Sarcoma?
38	(51398)	None	None	1, spindle, oval	None	No	No 5 yrs.	Sarcomatous changes?
39	(59317)	None	None	1, spindle, oval	None	No	No 7 yrs.	Degenerative sarcoma?
40	(59762)	None	None	1, mixed	None	No	No 5 yrs.	Sarcomatous degeneration
41	(5214)	None	None	2, mixed	None	No	No 5 yrs.	Fibroma, sarcoma or myosarcoma?
42	(75009)	None	None	1, mixed	None	No	No 6 yrs.	Sarcomatous
43	(76996)	Very few	...	2, spindle, oval	None	No	No 18 mos.	Sarcoma?
44	(8314)	Very few	...	1, mixed	None	No	No 5 yrs.	Cystic degeneration
45	(9437)	Very few	...	1, spindle, oval	None	No	No 2 yrs.	Hemangioma
46	(12534)	None	None	2, mixed	None	No	No 2 yrs.	Secondary hyperplasia
47	(17077)	None	None	1, spindle, oval	Few	No	No 2½ yrs.	Secondary hyperplasia
48	(18071)	Very few	...	2, spindle, oval	Few	No	No 2 yrs.	Fairly cellular
49	(18685)	None	None	2, spindle, oval	None	No	No 2 yrs.	Secondary hyperplasia
50	(189824)	Very few	...	2, round, oval	None	No	No 9 mos.	Early myosarcoma
51	(194310)	None	None	2, spindle, oval	None	No	...	Cellular
52	(197431)	Very few	...	1, spindle, oval	None	No	3½ mos. (Note 5)	Cellular
53	(207489)	None	None	1, spindle, oval	None	No	...	Cellular
54	(208063)	None	None	1, spindle	None	No	...	Cellular
55	(220349)	Very few	...	1, mixed	None	No	?	Cellular
56	(224532)	Very few	...	2, mixed	None	No	Metastasis	Early sarcoma
57	(228619)	Very few	...	2, mixed	None	No	...	Fairly cellular
58	(228653)	Very few	...	1, irregular	None	No	No 15 mos.	Secondary hyperplasia
59	(237267)	None	None	1, spindle, oval	None	No	...	Cellular areas, secondary hyperplasia
60	(243528)	None	None	1, irregular	None	No	No 1 yr.	Very cellular
61	(248302)	None	None	2, spindle, oval	Few	No	No 7½ mos.	Cellular
62	(254173)	None	None	1, spindle	None	No	No 7 mos.	Myosarcoma (Note 6)
63	(258667)	None	None	1, spindle, oval	Few	No	No 7 mos.	Cellular, probably early sarcoma
64	(258698)	Very few	...	1, round, spindle	Few	No	No 5 mos.	Spindle-cell sarcoma.
65	(258852)	None	None	1, irregular	None	No	...	Fairly cellular
66	(259958)	None	None	2, irregular	None	No	...	Fairly cellular
67	(175048)	No specimen	...	...	...	No	...	Fairly cellular
68	(199649)	No specimen	...	...	...	No	...	Cellular, degenerating
69	(205331)	No specimen	...	...	...	No	...	Very cellular
70	(247484)	No specimen	...	...	...	No	19 mos.	No examination
71	(250107)	No specimen	...	...	...	No	No 9 mos.	...
72	(207995)	No specimen	...	...	...	No	Inoperable	...



TABLE 2.—FREQUENCY OF NON-EPITHELIAL MALIGNANT UTERINE TUMORS AS COMPARED WITH FREQUENCY OF FIBROIDS

	Fibroids	Malignant	Percentage
Proper and Simpson.....	357	22	6.00
Miller.....	9750		1.96
Lewis.....	1518		1.40
Olshausen.....	6470		1.30
Kelly and Noble.....	2274		2.00
Winter.....	500		3.20
Winter.....	253		4.30
Noble.....	337	2	0.60
Kelly and Cullen.....	1400	17	1.20
Martin.....	205	4	1.90
Fehling.....	409	8	1.90
Broun, Woman's Hosp., N. Y.	1500	7	0.40
Warner.....	100	Including all "cellular" "Sarcomas" only, 7	7.00
Geist.....	250	2	2.00
Present series.....		12	4.80
1917-1918.....	968	Group 1 6	0.62
		Groups 1 and 2 12	1.25
		Groups 1, 2, and 3 38	4.00
1906-1918.....	3297	Group 1 13	0.39
		Groups 1 and 2 22	0.67

TABLE 3.—MORTALITY PERCENTAGES FOR CONSECUTIVE OPERATIONS FOR REMOVAL OF FIBROIDS OF THE UTERUS

	Cases	Mortality, per cent
Woman's Hospital, New York (Broun).....	1500	1.86
Woman's Hospital, New York (1918).....	262	1.53
Deaver.....	750	1.73
Frank and Brettauer.....	400	1.75
St. Mary's Hospital (Mayo Clinic, 1916, 1917, and 1918).....	1188	1.18
St. Mary's Hospital (1912-1918).....	2774	1.59

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## STUDIES ON ORGAN TRANSPLANTATION

### I. TRANSPLANATION OF THE THYROID GLAND WITH INTACT BLOOD SUPPLY\*

K. KAWAMURA

There are two methods of free grafting of a gland: the transplantation of pieces of tissue, and the transplantation of the whole organ with anastomosis of its blood vessels to those of the same person or of another person. In 1892 von Eiselsberg transplanted the thyroid gland in a cat. He removed half of the gland and transplanted it into the abdominal wall. Several weeks later he extirpated the other half of the gland. The animal remained in good condition but died when the transplanted thyroid was removed. Since that time many instances of thyroid grafting, both experimental and clinical, have been reported, and it has been shown that thyroid grafts in animals take and functionate.

Fairly effective results were obtained by Cristiani (1904, 1906) after transplantation of thyroid tissue in the subcutaneous cellular tissue, by Payr (1906) after transplantation in the spleen, and by Kocher (1914) after transplantation in the bone marrow. On the other hand, there are also many reports of negative results. Enderlen considered the functional activity of transplanted thyroid limited and temporary, as a consequence of his experiments in which cats and dogs died even after a period of six months. Bircher, Leichner and Köhler, Stieda, and others implanted thyroid gland into the subcutaneous tissue or bone marrow of patients, with no permanent improvement. In 1914 von Eiselsberg reported the transplantation of thyroid and parathyroid in man. It seemed to him at first that the grafting was effective, but all efforts finally proved unavailing. He believes that the function of the transplanted pieces of glands is probably only temporary.

The development of vascular surgery has made it possible to transplant whole organs with their related vessels. In 1905 Carrel and Guthrie extirpated the thyroid gland of a dog, placed it in isotonic salt solution for a few minutes, and replaced it into the neck, anastomosing the blood vessels but with reversal of the circulation. The arterial blood entered the gland through the thyroid vein and the venous blood flowed from the gland to the jugular vein through the thyroid artery. Eleven days after the operation an exploratory opening of the neck was made. The color and consistency of the gland were normal. Eight months after the operation the gland was normal in

\* Reprinted from *Jour. Exper. Med.*, 1919, xxx, 45-63.

size and consistency. Later, Carrel (1909) extirpated a large parenchymatous goiter in a dog and replanted it. He then cut transversely the common carotid and united its central end to the peripheral end of the internal jugular. The central end of the jugular was sutured to the peripheral end of the carotid. The size of the gland increased enormously. At the same time, clear fluid exuded from the surface of the gland but diminished and stopped completely after more than a week.

Stich and Makkas performed a series of thyroid transplantations. After the dissection of the upper thyroid artery to the point of its departure from the common carotid, they resected a rhomboid flap of the carotid in connection with the thyroid artery and inserted it in the corresponding hole of the other carotid. The internal jugular vein was cut transversely just beneath its union with the lower thyroid vein, and sutured with the external jugular vein by end-to-side or end-to-end anastomosis. At the same time the other half of the gland was extirpated to obtain, immediately, sufficient function for the transplanted thyroid. Of three autoplasic transplantations, two were positive; that is, fifty-one and two hundred and forty-five days respectively after the operation the circulation was intact and the gland, both macroscopically and microscopically, was normal.

The gland was transplanted seven times homoplastically, but no positive result was obtained. An obstruction was almost always found at the point of the venous anastomosis, which brought about necrosis and reabsorption of the gland.

Borst and Enderlen similarly transplanted the thyroid of dogs and goats. Their method differed somewhat from the procedure employed by Stich and Makkas in that they used, for the grafting of the thyroid artery, the complete segment of the carotid with the thyroid artery. In seven instances they extirpated the thyroid and replanted it in the same animal. In two of the seven animals (twenty and one hundred twenty-two days after operation) the glands were in good condition. In the other animals necrosis, hemorrhagic infarct, degenerative metamorphosis, and so forth, took place, due to the thrombosis of the thyroid vein. They attempted homoplastic transplantation seven times (in dogs and goats), but none was successful. They also attempted in three instances to transplant the thyroid from man to man by the employment of blood vessel sutures. The upper pole of the gland was transplanted into the axilla of the elbow. The results in every case were fruitless.

Goodman also investigated this problem. He made a biterminal suture of a segment of the attached carotid of the severed vessel of the host, and an end-to-end suture of the thyroid vein with the central end of the external jugular of the opposite side. He performed three autoplasic and twenty-seven homoplastic transplantations, and observed them from twenty-four hours to one hundred twelve days after the operation. In autoplasic transplantation he succeeded in two instances (the duration of life was four and twenty-three days respectively) in retaining the thyroid gland in its normal state; while in homoplastic transplantation the gland remained intact for a short time only, and then showed evidence of absorption.

The results of the investigations with regard to thyroid transplantation as reviewed in the literature did not seem uniform and we were therefore induced to investigate the problem further. We chose for our experiments the transplantation of the gland through blood vessel sutures because of the favorable restoration of the circulation of the gland by this method.

## EXPERIMENTS

All the experiments were performed on dogs. Since the relation of the thyroid to its vessels in the dog is different from that in man, it may be well briefly to note this difference before the technic is described. In a dog the glands are spindle-shaped, situated beside and beneath the larynx, usually separated from each other, and more or less covered with muscle. The dog, especially the bulldog, has a relatively large thyroid, which is not always proportional to the size of the animal; a small dog may have remarkably large glands due to the development of the so-called colloid goiter. The arterial blood reaches the gland mainly through the superior thyroid artery, which arises from the common carotid and enters the gland at its upper pole after having made an upward convex curve. Very rarely this artery enters the gland near its middle and ramifies with many branches. The inferior thyroid artery is very small; accordingly it may usually be ignored in the transplantation of the thyroid. The venous blood flows out through two veins, the superior and inferior thyroid veins. The superior thyroid vein leaves the upper pole of the gland and empties into the internal jugular vein, while the inferior thyroid vein, consisting of two stems, opens into the same vein further down. The diameter of the superior thyroid artery and thyroid veins is scarcely greater than 1.5 to 2.5 mm. It is, therefore, almost impossible to anastomose these vessels.

The operation was performed under intratracheal ether anesthesia. The Carrel (1907) technic of blood vessel suturing was employed, and special attention was paid to rigid asepsis. A longitudinal median incision was made in the neck and the superficial muscles were separated. The thyroid gland was dissected from the surrounding tissue, the superior thyroid artery and superior and inferior thyroid veins being left intact. In most instances the gland was extirpated with a portion of the internal jugular vein and a segment of the common carotid artery, connecting the thyroid veins and the superior thyroid artery respectively. The gland was immediately wrapped in a sponge saturated with warm salt solution. After a few minutes the gland was transplanted to the other side of the neck of the same dog, or into the neck of another dog, where the thyroid had been previously removed. The segment of common carotid was inserted in the place of the other below the point of outlet of the thyroid artery.

The peripheral end of the internal jugular vein was united to the central end of the internal or external jugular vein of the recipient by end-to-end anastomosis. In one case the gland with a rhomboid flap of the carotid at the point of outlet of the superior thyroid artery was removed (Stich's so-called patching method) and replaced in the wound in the neck. In two animals the peripheral end of the internal jugular vein was united to the wall of the external jugular vein (end-to-side). Moreover, in 2 cases, after resection of half of the spleen, the thyroid was transplanted to the splenic vessels of the same animal. In these instances the superior thyroid artery was sutured to the splenic artery, and the internal jugular vein to the splenic vein by end-to-end anastomosis. The time required for the extirpation of the gland and its complete transplantation was usually from one to two hours. The clamp on the vein was removed first and then that on the artery. As soon as the clamps were unfastened the gland became normal in color; it was somewhat distended. Several days after the operation the wounds were opened and the condition of the transplanted thyroid gland was examined. As a rule, if the gland appeared normal the other intact thyroid was fixed in 10 per cent formaldehyde for microscopic examination.

Both autotransplants and homotransplants of the gland were made, as shown in Table 1. A total of eight autoplasic and seven homoplasic transplantations was made. Two autoplasic transplants (Experiments 2 and 3) and one homoplasic (Experiment 9) are described.

*Experiment 2 (Dog 2).—Adult bulldog, male; weight 12 kg.*

Sept. 18, 1918. Placed under ether anesthesia and the right thyroid gland transplanted to the left side of the neck. The segment of the right carotid artery, from which the superior thyroid artery arose, was implanted by end-to-end anastomosis into the left carotid. The peripheral end of the right internal jugular vein was anastomosed to the cardinal end of the left external jugular vein. The excised gland had been left in a salt pack for a short time. After the removal of the clamps the pulsation of the superior thyroid artery was very evident and the circulation through the gland was reestablished so that it immediately became normal in color. The extirpation of the gland and its complete transplantation occupied one and one-half hours. The wound was closed according to the routine technic of the laboratory.

September 20. The animal was in good condition and had a normal appetite.

October 9. Second operation. The weight of the animal at this time was 13.1 kg. The transplanted thyroid appeared perfectly normal. The intact left thyroid was removed. The animal recovered from the operation and showed no signs of tetany.

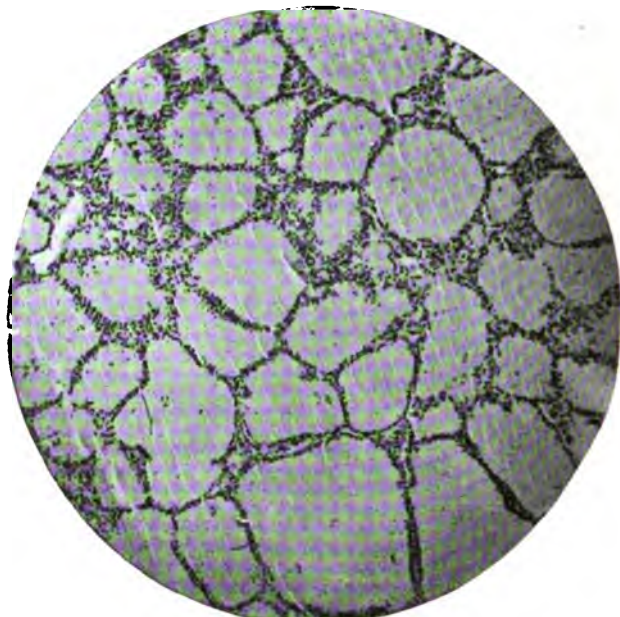


FIG. 192.—Photomicrograph of intact left thyroid of Dog 2 ( $\times 70$ ).

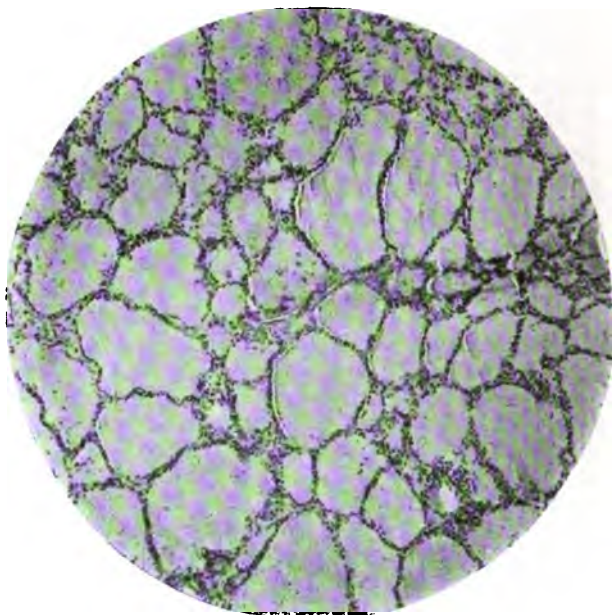


FIG. 193.—Photomicrograph of transplanted right thyroid of Dog 2 (autotransplant).  
Compare with the control in Fig. 192 ( $\times 70$ ).

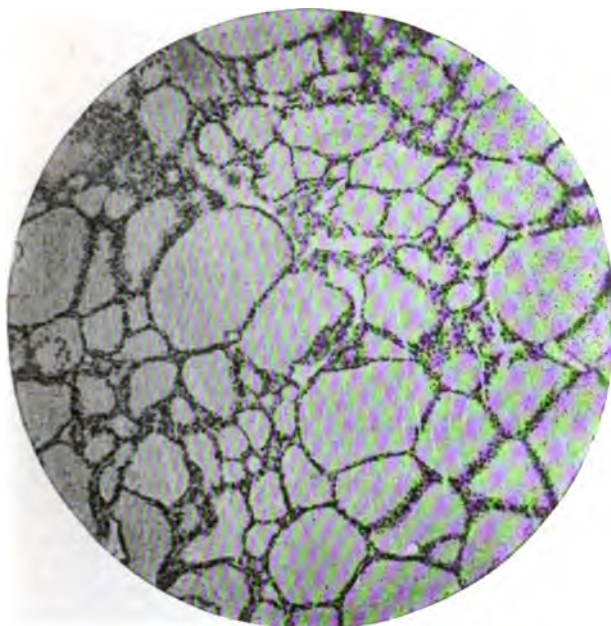


FIG. 194.—Photomicrograph of intact right thyroid of Dog 3 ( $\times 70$ ).

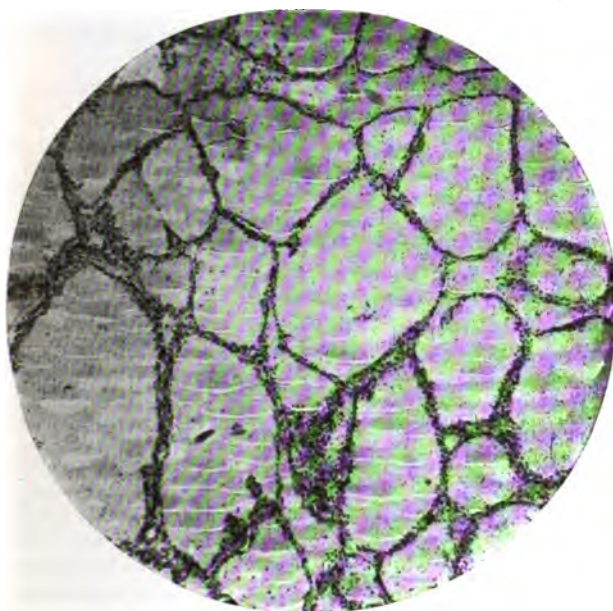


FIG. 195.—Photomicrograph of transplanted left thyroid of Dog 3 (autotransplant)  
Compare with the control in Fig. 195 ( $\times 70$ ).



October 29. The animal died early in the morning (forty-one days after the first operation and twenty days after the second).

*Necropsy.*—Performed shortly after death. The wound had healed completely; the cause of death could not be found. The transplanted thyroid was normal in size, color, and consistency and appeared normal on section. The capsule of the gland was not markedly thickened. The implanted blood vessels were patent. The lines of union were covered with epithelium and so smooth that they were found with difficulty.

*Microscopic examination.*—The transplanted thyroid showed no difference from the control gland. The capsule of the gland was not increased in thickness. The follicles were normal in size and about the same in both the central and peripheral parts of the gland; they were lined with cuboidal epithelium, and filled with a normal amount of colloid. The staining reaction was normal; mitoses were not present. The interstitial connective tissues were not increased as compared with the control specimen. Increase of blood vessels was not visible. No leukocytic infiltration could be found (Figs. 192 and 193).

*Experiment 3 (Dog 3).*—Adult collie, female; weight 21.3 kg.

Sept. 19, 1918. Etherized and the left thyroid gland transplanted to the right side of the neck. The gland was small, as was also the internal jugular vein. The left thyroid was displaced to the right with a segment of the common carotid and the internal jugular vein. The segment of the left carotid was inserted into the right carotid. The peripheral end of the left internal jugular vein was implanted into the wall of the right external jugular by a terminolateral anastomosis. The operation was difficult owing to the different sized vessels. Nevertheless, it was, on the whole, satisfactory. There was no leakage at the line of suture. The circulation was reestablished about one and one-half hours after the extirpation of the gland. The wound was closed in the routine manner.

October 9. Second operation. At this time the animal weighed 21.4 kg. The transplanted thyroid gland appeared normal. The intact right thyroid was removed and fixed in formaldehyde.

November 20. The animal died during the preceding night (sixty-two days after the first operation and forty-two days after the second).

*Necropsy.*—Performed shortly after death. The wound had healed by first intention; there were slight adhesions at the site of operation. The transplanted thyroid appeared entirely normal. The blood vessels were patent, and the site of anastomosis was in excellent condition. The cause of death could not be determined.

*Microscopic examination.*—The transplanted thyroid was practically normal. The thickness of the capsule of the gland was normal. No difference was seen in the size and form of the follicles, in the colloid content, or in the quantity of interstitial connective tissue, in comparison with the other gland of the same dog. Cuboidal epithelium lined the follicles as in the control section. The gland contained a large number of blood vessels. Here and there clumps of a few leukocytes were visible (Figs. 194 and 195).

*Experiment 9 (Dog 9).*—Adult mongrel, male; weight 5 kg.

Sept. 25, 1918. The left thyroid of another dog was transplanted, under ether anesthesia, to the left side of the neck by the insertion of a segment of the common carotid into the carotid. After the dissection and removal of the left thyroid gland, about 3 cm. of the left common carotid were resected. The peripheral end of the internal jugular vein of the donor was united to the central end of the external jugular of the recipient. The transplanted thyroid was very large, as was also the internal jugular vein. The operation was easily performed. After one and one-quarter hours

the circulation through the gland was reestablished satisfactorily. Closure of the wound was made as usual. The animal recovered from the operation but developed distemper.

October 1. The animal died during the night.

*Necropsy.*—Death due to distemper. Both the arterial and the venous anastomoses were in good condition; the caliber of the vessels was well preserved. The transplanted thyroid appeared normal in size, color, and consistency. On section it was normal in appearance except in the posterior border where the tissue was somewhat brown and was more gelatinous than the other part.

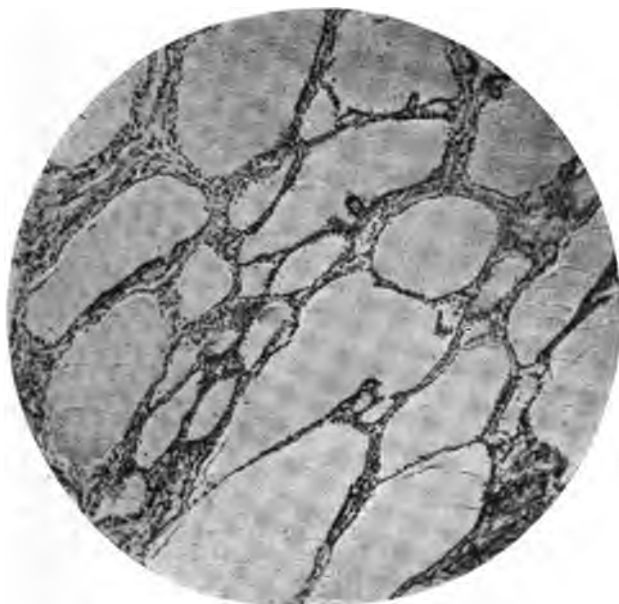


FIG. 196.—Photomicrograph of transplanted thyroid of Dog 9 (homotransplant) ( $\times 70$ ).

*Microscopic Examination.*—The capsule of the gland was more or less thickened. The interlobular septum also appeared to be thickened. The size of follicles and their colloid content were as well preserved as in the autografts. The staining reaction appeared normal. Few follicles contained desquamated cells in their lumen. Some of these cells were calcified. There was a small amount of leukocytic infiltration. The vascularization of the gland was normal (Fig. 196).

Eight autoplasmic and seven homoplasmic transplantations of the thyroid gland were performed. In two of the eight autoplasmic transplantations the gland was transplanted to the splenic vessels, in six to the neck. The first two dogs were examined by exploratory laparotomy twenty-one and twenty-eight days respectively after the first operation. It was found that the glands had become necrotic because of thrombosis. It seems almost impossible to get successful

TABLE 1.—SUMMARY OF EXPERIMENTS

Experiment No.	Operation	Duration of observation	Results			Remarks
			Condition of blood vessels	Condition of transplanted thyroid	Microscopic examination	
Autoplastic transplantation						
1 (Dog 1)	1918 September 11. Transplantation of right thyroid with a segment of common carotid to left side. October 30. Exploratory opening of neck.	Days 49	Left common carotid pulsating everywhere; superior thyroid artery and inferior thyroid vein thrombosed.	Entirely absorbed.		At first operation great hemorrhage from peripheral end of right common carotid due to slipping ligature. Lower part of wound slightly infected. Dog still living. October 29. Died.
			Arterial and venous lumen patent. Line of union covered with endothelium, and smooth. No thrombosis or clots.	Size, color, and consistency absolutely normal.	No necrosis. Appeared normal.	
			Arterial and venous lumen patent. Line of union smooth. No thrombosis or clots.	Appeared entirely normal.	No necrosis. Appeared almost normal.	
2 (Dog 2)	September 18. Transplantation of right thyroid with a segment of common carotid to left side. October 9. Extirpation of the original left thyroid.	61				
3 (Dog 3)	September 19. Transplantation of left thyroid with a segment of common carotid to right side. Termino-lateral anastomosis between left internal and right external jugular vein.	62				November 30. Died.

4 (Dog 4)	September 21. Transplantation of left thyroid with a segment of common carotid to right side. Termino-lateral anastomosis between left internal and right external jugular vein.	4	Arterial anastomosis in good condition. Very small clot at mouth of external jugular vein.	Almost same size as the other. Fairly dark and hard but mostly translucent.	Almost normal with exception of a few congested blood vessels.	Both thyroids small. Congestion of venous blood at the point of anastomosis due to a bend of transplanted internal jugular vein which was too long. Animal died of distemper.
5 (Dog 5)	September 23. Replacement of left thyroid. Rhomboid flap was taken from left common carotid. October 9. Exploratory opening of the neck.	18	Arterial suture intact, but vein stopped up.	Normal size; soft. Surface of section pale, not translucent.	Follicle and colloid entirely disappeared.	Both thyroids very small. October 11. Died.
6 (Dog 6)	November 29. Replacement of right thyroid with a segment of right common carotid.	1	All sutures in good condition.	Appears normal.	Abundant leukocytic infiltration and proliferation of connective tissue. Almost normal; a few leukocytic infiltrations.	November 30. Died. Cause of death unknown.
7 (Dog 7)	December 16. Resection of half of spleen. Transplantation of left thyroid into splenic vessels. Jan. 13, 1919. Exploratory laparotomy.	28	Obstruction at point of arterial anastomosis.	Normal size but dark in color. Whole gland necrotic.	Necrosis.	Superior thyroid artery entered at the middle part of the gland.
8 (Dog 8)	December 23. Transplantation of right thyroid into splenic vessels. Jan. 13, 1919. Exploratory laparotomy.	21	Obstruction at point of arterial anastomosis; thrombosis in vein.	Gland diminished to size of tip of thumb. Surface of section anemic; no blood came out.	Necrosis.	At the first operation spleen not resected.

'19 - 25.

TABLE I—*Concluded*

Experiment No.	Operation	Duration of observation	Results			Remarks
			Condition of blood vessels	Condition of transplanted thyroid	Microscopic examination	
Homoplastic transplantation						
9 (Dog 9)	1918 September 25. Transplantation of left thyroid with a segment of common carotid of left neck. Internal jugular vein united to external jugular.	Days 6	Line of suture in good condition. Caliber of artery and vein patent.	Size, color, and consistency almost normal. Longitudinal section showed a thin brownish and somewhat gelatinous part along the posterior border.	Almost normal. Septum between follicles increased more or less in thickness. Follicles filled with colloid. Deposit of lime and loosened epithelium visible here and there in follicles.	Both glands very large. October 1. Animal died of distemper.
10 (Dog 10)	September 26. Transplantation of left thyroid with a segment of common carotid to right neck. Ends of internal jugular vein united to each other by end to end anastomosis.  October 14. Exploratory opening and proof excision of the gland.	18	Right common carotid pulsating everywhere.	Gland kept its original size; color pale red. No hemorrhage on incision.	Interstitial tissues increased. Follicles filled with leukocytes, detritus, and fibrin. Here and there deposit of lime.	

11 (Dog 11)	September 27. Transplantation of right thyroid with a segment of common carotid to left neck. October 14. Exploratory opening. Extirpation of right intact thyroid.	24	Thrombosis in common carotid. Obstruction of internal jugular vein along the suture line.	Gland kept almost original size; softer than normal. Cut surface brown, dim, not translucent.	Capsular thickening. No trace of follicles or coloids.	At second operation the veins on anterior portion of gland were visible and filled with blood.
12 (Dog 12)	September 28. Transplantation of left thyroid with a segment of common carotid to left neck.	63	Transplanted common carotid and internal jugular vein obstructed.	Entirely disappeared.		October 21. Animal died with typical symptoms of tetany.
13 (Dog 13)	September 30. Transplantation of left thyroid with a segment of common carotid to left neck.	5	Thrombosis in common carotid and inferior thyroid vein.	Enlarged; cut surface dark red.	Septum increased in thickness. Follicles filled with detritus and fibrin. Nuclear staining weak.	A week after first operation large hematoma formed in the neck. October 5. Died.
14 (Dog 14)	October 1. Transplantation of right thyroid with a segment of common carotid to left neck. October 30. Exploratory opening.	29	Thrombosis in common carotid.	Atrophy of gland to size of tip of little finger.		Caliber of internal jugular vein very small.
15 (Dog 15)	October 4. Transplantation of right thyroid with a segment of common carotid to left neck. October 30. Extirpation of right intact thyroid.	27	Thrombosis in common carotid, in inferior thyroid vein, and in internal jugular vein.	Diminished to size of tip of thumb. Consistency soft.	Follicles and colloid entirely disappeared. Here and there clumps of lymphocytes. Abundant proliferation of connective tissue.	Animal died with symptoms of tetany day after second operation.

results by anastomosing such a small vessel as the superior thyroid artery to the splenic artery. Two of the six transplantations to the neck were replaced in the same wounds, and four were made to the other side of the neck. One of these was examined eighteen days after the operation and obstruction of the transplanted vein and necrosis of the gland were found. One transplant was examined forty-nine days after the operation. The gland had entirely disappeared, and the superior thyroid artery and the inferior thyroid vein could not be found, though the pulsation of the common carotid was very evident throughout. The failure was due to infection of the wound. In four instances (one, four, forty-one, and sixty-two days after the operation), all blood vessels were patent, and the gland appeared, both macroscopically and microscopically, to have preserved its normal structure.

Seven of the homoplastic transplantations were examined in periods of five, six, eighteen, twenty-four, twenty-seven, twenty-nine, and sixty-three days after the first operation. In two the segments of the carotid remained free from thrombosis and were covered smoothly with endothelium, although in five instances the transplanted vessels, in whole or in part, were occluded. The thyroid gland showed evidences of remarkable change in proportion to the time elapsed. Six days after the operation the gland retained its original size, and for the most part, was translucent, but in a part of the posterior border the tissue was beginning to soften. Microscopic examination showed that the size of follicles and colloid content were as well preserved as in the autograft. In the gland which was examined eighteen days after the transplantation, the consistency was markedly soft, the color of the section was pale red, and no hemorrhage had occurred at that time, notwithstanding the fact that the gland kept its original size and the carotid was still patent. Microscopic examination showed great degeneration of the gland. After twenty-four days the microscopic change of the gland increased, and it became gradually smaller. In one case, sixty-three days after the operation, no trace of the gland was to be found. In brief, our attempts at homoplastic transplantation were unsuccessful.

#### DISCUSSION

Our results in thyroid transplantation by blood vessel sutures agree on the whole with the experiences of Stich and Makkas, Borst and Ender-

len, and Goodman. In the autoplasmic transplantations we succeeded, as they did, in maintaining the glands for a long time in their original shape and structure, and apparently in function. In the series of homoplasmic transplantations, on the contrary, the transplant remained intact for a time, then underwent degenerative changes, and, consequently, absorption.

Hesselberg has published a paper concerning a comparison of autoplasmic and homoplasmic transplantation of thyroid tissue in guinea pigs. She transplanted pieces of glands into the subcutaneous tissue of the abdominal wall and examined them at intervals of from twenty-four hours to fifty-two days. In the first stage, comprising the first four to five days, there was no noticeable difference between the autografts and the homografts. Large parts of both grafts became necrotic in the center, but in the peripheral part only a narrow zone of thyroid tissue was left. In the second stage, extending over the next seven days, the differences between the two grafts appeared. There was an increase in the number of follicles in the autografts and a corresponding decrease in the size of the necrotic central area. In the homografts a large number of lymphocytes and connective tissue were visible. From the twelfth day on, in the third stage, the difference between the grafts was sharply defined. In the autograft the regeneration of the thyroid tissue was steadily progressing and nearly completed after twenty-one days. In the homograft, on the contrary, the destruction of the follicles progressed with great intensity.

Loeb (1918-1919) recently designated the transplantation into nearly related animals and to the nearly related of the same species as "syngenesioplasmic" transplantation. He carried out transplantation of thyroid from mother to children, from sister and brother to sister or brother, and in one instance from child to mother in guinea pigs. The results were intermediate between those which Hesselberg obtained after autotransplantation and homotransplantation. In most instances the thyroid behaved, for a time, like an autotransplanted tissue, but gradually an intensive lymphocytic infiltration took place with secondary destruction of the healthy acini. In a smaller number of cases the fibrous tissue also was increased, the fibroblasts behaving like those in cases of homoplasmic transplantation.

In one of our cases of homoplasmic transplantation also (Experiment 9) the gland showed indications of degeneration on the sixth day after the operation, in spite of the fact that the transplanted blood vessels were patent. The destruction of the gland increased in the process of time.

Homoplasmic transplantation, however, can be successfully made in certain kinds of tissue. At the instant the animal dies the tissues, in general, do not lose their vitality in spite of the arrest of the circulation. On the other hand, individual tissues have a different power with regard to regeneration and repair. Some tissues, such as skin, fascia, periosteum, and bone, which survive for a long time under the interruption of the circulation, can regenerate and repair easily.



Such tissues, as is well known, can be transplanted homoplastically with success although the ultimate fate of the transplant is not fully known.

As has been noted, the opinions of authors differ with regard to the fate of the more highly organized tissues, such as the thyroid gland. Cristiani has shown that transplanted and functioning thyroid may be kept in good condition in its new location for a long time, provided the operation is performed with certain precautions. For the successful transplantation, he emphasized that the pieces of gland transplanted must be small and numerous, that thyroid tissue from the same species only will grow, and that living tissue may be transplanted, provided that not more than ten seconds elapse between the extirpation of the tissue and its transplantation. Cristiani applied also, clinically, the results of his experimental work, and from his experience on patients arrived at the following conclusions: With his method of thyroid grafting it is possible to produce new thyroid organs which not only retain their vitality and functionate, but gradually grow so that small grafts in time become new thyroid glands (*glandulae neothyreoideæ*) of different sizes.

Payr (1906) transplanted thyroid gland into the spleen of animals, believing that spleen is suitable soil for healing because of its vascular nature. Of 48 experiments of autoplasmic transplantation, mostly on cats and dogs, he obtained eight promising results. The longest duration of the observation was two hundred seventy-one days. He had likewise made the transplantation of the thyroid gland clinically. A few years ago he reported 7 cases of thyroid transplantation for myxedematous patients; they showed marked improvement, but most of them relapsed from three to eight years after the operation. He remarked that organic cerebral defects of patients cannot be improved by thyroid grafting.

Kocher reports several favorable cases of transplantation of pieces of thyroid in patients, using the bone marrow as new soil. He prefers the tibial metaphysis to the spleen on account of the greater ease and safety of the operation and the equally vascular soil; hemostasis is secured by operating in two stages. With regard to the tissue for transplantation: Pieces from exophthalmic goiter are especially desirable, because the glands are remarkably vascular with comparatively firm structure, and because their proper parenchyma surpasses considerably the supporting substance. He stated that there are no grounds for the belief, based on animal experiment, that homoplastic transplantation cannot also succeed in man.

There are some reports of conflicting opinions with reference to these favorable results. Bircher implanted pieces of thyroid into the subcutaneous tissue of the occipital region in three cretins. After short improvement there was relapse into the former state. On histologic examination of the grafts he found that no normal thyroid tissue was left, but necrosis and connective tissue had replaced the whole. His observations made him skeptical as to the permanent function of homoplastic implanted thyroid. Lechner and Köhler were of the same opinion as Bircher. Stieda reported 3

cases in which the grafting was done on myxedematous children who were more or less idiotic. After operation they showed signs of remarkable, rapid improvement, which shortly came to a standstill. Schaack and Müller repeatedly transplanted thyroid tissue into the bone marrow or into the subcutaneous tissue, with no permanent improvement. The thyroid grafts which Worobjew and Perimow made on a myxedematous patient healed, but subsequently became smaller and were totally absorbed. von Eiselsberg (1914) also, from his experience with patients, expressed doubt that successful results could be obtained.

Thus, while some observers admit the feasibility of thyroid grafting, others deny it. The negative results of our experiments do not warrant denial of the positive results of Cristiani, Payr, Kocher, and others, but, as Bircher has already noted, we should not lightly pass over the possibility that implanted pieces of tissue will have an influence as long as the colloid exists, that its absorption occurs very slowly, and finally, that the moment the colloid is absorbed its influence stops. Furthermore, although many successful cases of piecemeal homoplastic transplantation on patients have been reported, they are not always without objection, because one important factor is wanting in all, namely, the subsequent removal and microscopic examination of the tissue. In short, for permanent good results we must expect to work further in this direction. Several points must be considered in the successful take of transplanted tissue: (1) The avoidance of injuring the tissue, and a sufficient blood supply. In this connection the transplantation with intact blood supply is the better method. (2) In the organ transplantation, especially by means of blood vessel sutures, aseptic precaution must be observed as rigidly as possible; If not, the occlusion of the transplanted vessels or necrosis of the organ may easily occur. Concerning asepsis in operations on blood vessels Carrel (1907) states: "it seems that the degree of asepsis under which general surgical operations can successfully be performed may be insufficient for good results in vascular operations." In our first case of autoplasmic transplantation the results immediately after the operation were satisfactory, but the lower part of the wound was, unfortunately, slightly infected. At the exploratory opening of the neck forty-nine days after the operation, we found that the transplanted common carotid was patent, but that the gland had entirely disappeared, due to infection.

Besides, the rapid work, keeping the gland warm, the avoidance of dryness, rough handling, chemical irritation, close contact with the new soil, and strict arrest of hemorrhage, are all apparently necessary

conditions for a good transplantation. If these precautions are used autoplasmic transplantation is almost always successful. But we failed, as did the others, in homoplasmic transplantation, notwithstanding the fact that we used similar care. The factors that may have been responsible for the failure are briefly the following:

It is well known that nerves have some control over the nutrition and function of tissues. Raynaud's disease, for example, is supposed to be due to spasm of the arterioles, resulting from peripheral neuritis. If a nerve trunk is injured severely and the peripheral end undergoes degeneration, several phenomena may occur, due to the loss of the trophic function of the nerve, such as dryness of the skin, trophic ulcers, fragility of the nails and hair, and arthropathies. It seems to be reasonable, therefore, to suppose that the failure of the graft can be attributed to the section of the nerves which reach the organ.

Crowe and Wislocki in experimental work on suprarenal glands in dogs attributed degenerative changes of the graft to the lack of nerve supply to it. We do not, however, fully concur with their opinion. Salzer and others also emphasize the independence of grafts from the nervous system. Manley and Marine, in considering the question of whether or not secretory nerves were necessary to the gland, experimented on rabbits. They have demonstrated that such nerve fibers are not essential in order that thyroid tissue may exhibit the characteristic morphologic and physiologic changes known to be associated with great variations in functional activity. Other authors have also found that thyroid tissue may be readily transplanted in widely distant parts of the body. In our experiments on autoplasmic transplantation we obtained good results in spite of complete dissection and removal of thyroids from their surrounding tissues. We cannot therefore consider that the failure of homoplasmic transplantation of the thyroid is due to the section of its nerves.

Murphy tried to prove that a homoplasmic or heteroplasmic graft cannot develop indefinitely on its host. He discovered that the power of the organism to eliminate foreign tissue is due to organs such as the spleen or bone marrow, and that when these organs are less active (by removal of the spleen or the injection of benzol) a foreign tissue (tumor) can develop rapidly after it has been grafted. The grafts became absorbed from twelve to fifteen days after the transplantation.

Hesselberg and Loeb attached a peculiar significance to lymphocytic reaction and to proliferation of connective tissue. They believe that the destruction of the thyroid tissue which occurs after the homografting is not caused by a direct primary disintegration or the solution of follicles, due to the action of substances circulating in the body fluids, but depends on the destructive activity of the lymphocytes, and of the connective tissue of the host. The former invade the follicles and destroy them directly; the latter surrounds and compresses, and thus destroys the follicles. Why do the lymphocytes and the connective tissues attack the homografts only, and not the autografts? It is well known that lymphocytes and connective tissue appear usually as the response to the reaction of foreign bodies. They may be commonly discovered around suture materials, such as silk and linen thread, that have been used in operations. It is reasonable, therefore, to assume that homografts which do not take may act as foreign bodies.

The obstacle to success in homoplastic transplantation lies probably in the differences of biochemic factors between the animals. As Ullman expresses it, the cell protoplasm, specific for each organism, varies with the individual; there are as many protoplasms as there are individuals; in homoplastic transplantation the appearance in the body of a foreign protoplasm calls forth ferments into the circulation which destroy the transplanted tissue.

Stich enumerated the following factors as the cause of the destruction of the grafts: primary toxic action of the tissue fluid on transplanted organs; production of an antibody in the organism of the host through foreign albumin; and finally, starvation of the transplanted tissue, owing to the incapacity of the assimilation of materials that are necessary for its growth.

We are still ignorant of the means of eliminating these factors. Lexer (1914) showed that he had succeeded in overcoming some of the biochemic reactions between his animals by prolonged preliminary treatment of the host with tissues and blood serum taken from the donor. He considered that the possibility of the improvement of homoplastic surgery was most hopeful along this path. Schöne believes that positive results may be obtained in animals through the same nourishment and the same mode of living for a long period of time. Sauerbruch and Heyde demonstrated that direct communication of blood vessels was proved between parabiotic rabbits, and that substances which are soluble in blood, iodine, strychnine, and so forth, and even bacteria, go from one animal to the other through newly formed vascular channels. The question of whether or not products of metabolism of one animal are pernicious to another has not been solved. Enderlen and his collaborators aimed to make the biochemic differences equal by direct blood vessel anastomosis in dogs, but they could not attain their object. In short, it seems to be most important to discover the method of equalizing as nearly as possible biologic differences between donor and recipient.

#### CONCLUSION

Our experiments on dogs showed that the thyroid gland which was autoplastically transplanted, by means of various methods of blood vessel anastomosis, could live in good condition and functionate favorably several months after the operation, even after the interruption of the circulation for one and one-half hours. They further showed that the circulation through the transplanted blood vessels as well as glands was as good as normal, and that permanent successful results of the homoplastic transplantation of the gland are as yet not possible.

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# ISOLATION OF THE IODIN COMPOUND WHICH OCCURS IN THE THYROID\*

## First Paper

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Despite the many years of investigation of the thyroid, some of the most fundamental problems concerning this ductless gland are still the subject of speculation and controversy, and the certain progress which follows quantitative knowledge has not yet materialized. Since quantitative values cannot be obtained by clinical observations alone, and since pathologic studies of the glands cannot of themselves solve the function of the thyroid, it becomes apparent that nothing short of the actual isolation in pure crystalline form of the chemical substance or substances within the gland, which are responsible for its activity, can furnish the necessary knowledge with which to gain quantitative relationship. Having accomplished the isolation in pure crystalline form of the active agents within the gland, quantitative results may be obtained and ultimate solution of the thyroid problem is within the power of the investigator.

### INVESTIGATION OF THE CHEMICAL CONSTITUENTS OF THE GLAND, WITH ISOLATION OF THE IODIN-CONTAINING COMPOUND IN PURE CRYSTALLINE FORM

Starting with fresh and desiccated thyroid the present investigation was at first concerned with the diffusibility of the iodine-containing compound. Iodine is not dialyzable from the thyroid proteins, and will withstand rather severe chemical treatment and still be undialyzable through a collodion sack in running water. In order to determine the stability of the iodine compound, various

\* No historical review of the chemical investigation of the thyroid is given in this paper. The reader is referred to the attached bibliography.

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hydrolytic processes were applied to the thyroid proteins. Among others the alcoholic alkaline hydrolysis used by Vaughan was tried and, with some slight modifications, was found to produce a deep seated hydrolysis without breaking off iodine from its organic combination. Furthermore, the hydrolysis so alters the iodine-containing compounds that about 70 per cent of the total iodine is dialyzable. Another change brought about by the hydrolysis is the solubility of the iodine compound in acid. About 50 per cent of the total iodine contained in the hydrolyzed products is soluble in acids, and 50 per cent is insoluble. The iodine in the acid-insoluble portion is to a large extent not dialyzable. The presence of iodine in organic combination and in non-dialyzable form was encouraging evidence of the stability of the iodine compound and invited further investigation.

The physical and chemical properties of the acid-insoluble group of hydrolyzed constituents will be described somewhat in detail, since this will bring out the chemical problems involved and some of the difficulties encountered.

An alkaline solution of the acid-insoluble constituents is dark brown, almost black, with a green fluorescence, and shows a Tyndall phenomenon with a beam of light. The non-diffusibility, fluorescence, and Tyndall phenomenon show that the solution is one of colloidal nature. Among the acid-insoluble constituents are fatty acids resulting from the original fat in the desiccated thyroid, and sulfur, which results from the decomposition of cystine. The solution has no characteristic odor other than a general fatty smell. The first step in the method of separating the iodine compound is to dry the acid-insoluble constituents, mix with infusorial earth, and extract with petroleum ether to remove fatty acids and sulfur.

Later it was found that fresh thyroid glands could be substituted for desiccated thyroid as a source of material, and that hydrolysis in alcohol was not necessary. Hydrolysis of the proteins may be carried out by use of aqueous sodium hydroxide alone, and the length of the time can be reduced to twenty-four hours. A quantitative separation of all fats, as the sodium soap may be effected, and a perfectly clear alkaline filtrate of the hydrolyzed thyroid proteins containing practically the entire iodine content of the gland is obtained. On acidification of this solution, a fine flocculent precipitate separates. If this precipitate is filtered off and dried, it is found to contain approximately 0.1 per cent of the total weight of the fresh glands used. It contains, on



the average, 26 per cent of the total iodine. The total iodine in the gland, therefore, is divided by aqueous alkaline hydrolysis into acid-soluble and acid-insoluble compounds. Approximately three-fourths of the total iodine-containing compounds are soluble in acid and only one-fourth insoluble. This proportion is remarkably constant during different times of the year, and in different samples of thyroid from various species. The significance of the figure is not entirely clear, but in all probability it represents the equilibrium existing within the glands between the completed iodine compound which possesses physiologic activity and the materials which are used by the gland in the building up of the substance. Physiologically tested, the acid-soluble hydrolyzed constituents are inactive, and the small portion which is precipitated by acid possesses the entire physiologic activity of the gland.

The solubility of the acid-insoluble iodine compounds in organic solvents varies, depending on the solvent used, the presence of water, whether or not acid is present, and the temperature. About 10 per cent of the total iodine is soluble in ethyl ether, but only a small amount is soluble in petroleum ether.

If desiccated thyroid has been used as a source of material the dry acid-insoluble products freed from fatty acids by extraction with petroleum ether are dissolved in sodium hydroxid and again acidified. If the aqueous hydrolysis has been used the precipitate obtained by acidifying the alkaline solution of hydrolyzed products is dissolved in sodium hydroxid and reprecipitated with acid. This precipitate is heavy, flocculent, and amorphous, and, when heated above 40 to 50°C. in aqueous solution, turns to a black, tarry mass. On cooling and drying it is found to be brittle and may be broken into a fine, dry, almost black powder. The dry powder is soluble in acid ethyl alcohol and aqueous solutions of sodium, potassium, and ammonium hydroxids and carbonates. It is in part precipitated from acid alcohol by the addition of sodium carbonate, the portion precipitated being a sticky, black, tarry mass. Most of the iodine-containing compounds are soluble in alcohol in the presence of sodium carbonate, so that this is a valuable aid in the gross separation of the black, tarry impurities from the constituents which contain iodine. However, some of the iodine is carried down by the sodium carbonate precipitation, showing that the iodine compound, although probably the same throughout all the different precipitates, is attached to various groups of compounds which possess different solubilities.

If barium hydroxid is added to the alcohol solution after removal of the sodium carbonate precipitate, practically all the rest of the dark-colored compounds are precipitated by the barium. This precipitate carries down varying percentages of iodine, depending on conditions. If the solution is made acid with hydrochloric acid before the addition of barium, a very high percentage of the iodine may be precipitated. If the solution is made alkaline with sodium hydroxid, a very small percentage may be carried down. Between these two limits the amount removed by the barium depends on the acidity and the temperature. Since the alcohol solution remaining after precipitation with barium is light straw-colored, the alcohol-barium-soluble constituents to which the iodine compound is attached are almost colorless.

Similar separations may be produced in aqueous solution. If the dark brown alkaline solution of the hydrolyzed products is acidified, almost all the color and iodine compounds are precipitated. Barium, calcium, and magnesium salts, added to an alkaline aqueous solution of the acid-insoluble hydrolyzed constituents, precipitate practically all the dark-colored compounds, leaving a very light-colored solution. This precipitation divides the iodine present; about one-half is precipitated by the alkaline earths and one-half is soluble.

These precipitation and solubility properties clearly show the nature of the material with which one has to work. It is a mixture of compounds in colloidal form, and the problem is not only one of separating a mechanical mixture. It was necessary to gain a clear insight into the chemical nature of the iodine compound and the other constituents before the separation of the two could be realized.

The most striking property of the acid-insoluble group of hydrolyzed products is their acidic nature. They may be dissolved in alkali and reprecipitated by acid without appreciable loss of iodine.

Many attempts were made to separate the iodine compound by its solubility and precipitation properties with various reagents. No specific precipitant was found. No difference in solubility was found which could be used to effect a separation. After many attempts to separate the iodine compound had failed, it became apparent that the compound was not present in free form, but was still firmly bound to some unknown substances.

Experiments showed that iodine was not broken off when dissolved in moderately strong sodium hydroxid. In the hope that heating

in aqueous sodium hydroxid might produce a further hydrolysis, the acid-insoluble constituents of the alkaline-alcoholic hydrolysis were heated several hours in 5 per cent sodium hydroxid. It was then found that treatment with sodium hydroxid, followed by precipitation with an acid, will not effect a separation of the iodine compound from the black colloidal impurities. The solubility of the compounds present which do not contain iodine closely parallels the solubility of the iodine containing compound, and, as far as alkali and acid are concerned, no appreciable separation can be brought about by alternate treatment with each.

Since the addition of a soluble barium salt to an alkaline solution of the acid-insoluble products of hydrolysis precipitates practically all the brown impurities and does not carry down all the iodine, this separation was investigated to determine whether the percentage of iodine in the acid-insoluble constituents could thereby be increased. The acid-insoluble constituents were dissolved in dilute sodium hydroxid, and barium hydroxid was added. The solution was heated in a nickel crucible at 100°C. for eighteen hours. This treatment produced a precipitation of the brown compounds, giving a light yellow filtrate of the barium-soluble constituents. Determination of the iodine content of the filtrate showed that about 50 per cent of the iodine present had been precipitated from the alkaline solution by barium hydroxid, and 50 per cent remained soluble. Sodium sulfate was added to the water solution containing the barium-soluble constituents, and the barium was removed as sulfate. The solution was then acidified, and a copious precipitate obtained which still retained iodine. The precipitate was filtered off and dried. Analysis showed that the percentage of iodine had been very materially increased by this treatment. The iodine in the starting material amounted to about 5 per cent; after treatment with barium, as outlined above, and reprecipitation with an acid, the iodine was found to be about 15 per cent.

The portion of the starting material which had formed a dark, flocculent precipitate with barium hydroxid was dissolved in sodium hydroxid and sodium sulfate. The barium sulfate was removed and the solution was acidified. A precipitate formed on the addition of the acid and when this was filtered off and dried it too was found to contain an increased percentage of iodine. By treatment with barium hydroxid the percentage of iodine contained in the hydrolyzed constituents of the thyroid proteins had been increased.

As this was the only material advance which had been made toward isolation of the iodine-containing compound, it was decided to investigate more fully the reactions involved between barium and the hydrolyzed products of the thyroid proteins. The two precipitates were dissolved in separate solutions of sodium hydroxide, barium hydroxide was added to each, and the solutions were heated in nickel crucibles for eighteen hours at 100°C. The insoluble portions were filtered off, the barium was removed as outlined above, the barium soluble constituents of each crucible were combined and again acidified, the precipitate was filtered off and dried, and analysis showed that the percentage of iodine present had increased in the barium-soluble portion to 26 per cent. With many misgivings the precipitation with barium and heating in a nickel crucible were again repeated. The iodine content of the precipitate obtained was 33 per cent. Still another treatment yielded a product containing 42 per cent of iodine. The amount of material now consisted of less than 200 mg. The success of the method, however, called for still further treatment. It was carried out in the same manner, and a precipitate containing 47.3 per cent of iodine was obtained. The character of the precipitate had changed and the color of the solution had almost disappeared. It seemed probable that some other method of purification could now be applied to the preparation containing 47.3 per cent iodine.

The material was dissolved in 95 per cent alcohol; solution was complete. The alcohol was evaporated on a water bath to a small volume, in the hope that some crystals might separate. By a chance, however, the dish containing the alcohol evaporated to dryness, and the dried precipitate was heated for about one hour after the alcohol had been driven off. It was thought that on the addition of more alcohol the white powder on the bottom of the dish would again be dissolved, and, possibly, crystals might still separate. More alcohol was therefore added, but a white incrustation on the bottom of the dish was insoluble in alcohol. I believed that this treatment had effected a further separation, that the iodine-containing compound was redissolved in the alcohol, and that the white incrustation represented impurities. It was filtered off. The weight of this white powder was 18.6 mg. It was dissolved in sodium hydroxide, and a portion of it was used to determine iodine, when it was found that the iodine amounted to 60 per cent. The white incrustation was, therefore, not an impurity, but the iodine compound itself. Its solubility in alcohol had

been changed by heating the residue left after evaporation of the alcohol. More of the acid-insoluble constituents resulting from hydrolysis of the thyroid proteins were treated in precisely the same manner, and about 200 mg. of the white residue were obtained. When this was dissolved in aqueous sodium hydroxid, precipitated by adding sulfuric acid and boiling, it was converted into fine white microscopic crystals. For reasons which will be given this iodine compound has been named "thyroxin," and it will be referred to by that name throughout the remainder of this article.

As the yield of thyroxin depended on the amount of desiccated thyroid which could be treated at any one time, it was decided to enlarge our facilities for the hydrolysis of desiccated thyroid, which, up to this time, had been carried out in glass flasks. An eleven gallon galvanized iron tank was constructed, which could take care of 500 gm. of desiccated thyroid at one time. The acid-insoluble constituents were obtained as before. They were dissolved in dilute sodium hydroxid, barium hydroxid was added, and the steps outlined above were carried out. No crystals of thyroxin were obtained.

The work from this point will be presented in a logical rather than a chronological order, as many months were spent in elucidating the factors which prevented the isolation of more crystals.

After working for fourteen months in an endeavor to repeat the first isolation of the crystals, it was found that there are five conditions which influence the isolation of thyroxin in pure crystalline form.

1. *Effect of temperature on precipitation with an acid.*—When the partially purified, iodine-containing constituents are precipitated by an acid, the precipitate is flocculent and amorphous. If this is heated to from 40 to 50°C., it assumes a fine, granular form which can be filtered and washed very readily. This procedure was followed because of the facility of handling the precipitate. Warming of the acid solution does not break off any iodine in inorganic form. If, however, this precipitate, which was prepared by warming the solution after the addition of the acid, is dissolved in alkali and heated with barium hydroxid, and the solution is again acidified, some iodine in the inorganic form may be found in the solution. If the precipitation by an acid is carried out in the cold, subsequent heating with barium hydroxid and reprecipitation does not break off iodine in the inorganic form.\*

\*Inorganic iodine has been tested for during this investigation by acidifying the solution with hydrochloric acid, adding starch and a few drops of sodium nitrite, producing a blue ring if inorganic iodine is present.

Since only one stage of this treatment could be carried out in one day, twenty-four hours intervened between the first acidification and warming of the solution and the second precipitation, after which iodine was demonstrated in the inorganic form in the filtrate. This time interval formed a convenient screen behind which the deleterious action of heat remained hidden for many months. This influence of temperature on acidification was one of the most important causes for the failure to separate more crystals. Fearing that a concentrated sodium hydroxide solution would destroy the iodine compound, we had been neutralizing the alkali which was used to effect the primary hydrolysis with sulfuric acid before evaporating off the alcohol. As the amount of free alkali remaining in the alcohol was variable, depending on the amount of ammonia which had been evolved and the amount of water and carbonate in the alkali, it frequently happened that slight excess of acid was added, so that the alcohol was evaporated off in the presence of a small amount of acid. This we finally showed has a very destructive action on partially purified thyroxine. In this connection it seems probable that the lack of physiologic activity of iodothyronine is explained by this action of acid on the iodine-containing compound. The iodine may not be broken off by treatment with acid, but the chemical properties, and undoubtedly the nucleus to which the iodine is attached, are altered so that the compound loses its physiologic activity.

2. *Effect of heating the alkaline hydrolysis solution in the presence of metal.*—At first the hydrolysis was carried out in glass flasks. When an eleven gallon galvanized iron tank was substituted, the hydrolysis was carried out apparently just the same, but it was found that with the metal the hydrolysis in an alkaline solution resulted in the breaking off of the iodine in the inorganic form. Investigation showed that in alkaline solution, iron, zinc, copper, tin, lead, German silver, and, in fact, all metals except nickel and the heavy metals, gold, silver, and platinum, break off iodine from its organic combination. A heavily enameled, cast iron kettle was found to give a satisfactory surface for a container in which to carry out the primary hydrolysis with sodium hydroxide in alcohol. Later this was replaced by a nickel kettle.

3. *Effect of carbon dioxide.*—During the first separation of crystals carbon dioxide was neither employed directly nor was its effect excluded from the various steps in the process. After many months of failure to separate more of the iodine compound in crystalline form it was

found that carbon dioxid plays an important rôle in the separation of thyroxin from the impurities. By chance an alkaline solution containing a partially purified preparation of thyroxin mixed with a large amount of impurities was precipitated with carbon dioxid instead of with sulfuric acid. The precipitate was filtered on a Buchner funnel and washed with distilled water. Instead of the distilled water running through lighter colored than the first filtrate, it was almost black (Fig. 197). Investigation showed that the black impurities

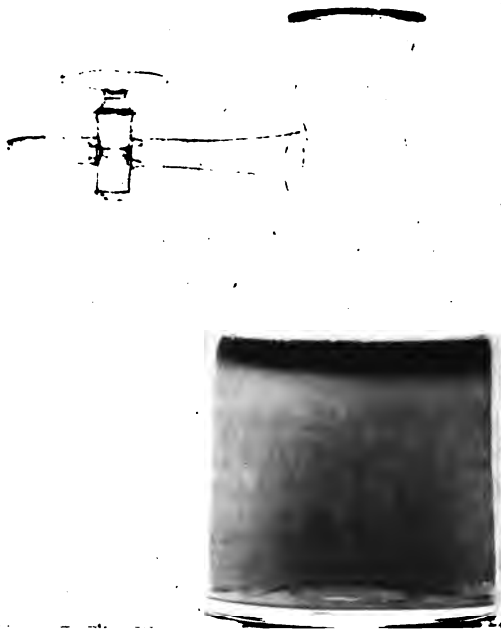


FIG. 197.—Suction flask showing the color change which led to the investigation of the effect of carbon dioxid on the separation of thyroxin.

were insoluble in water saturated with carbon dioxid but were soluble in distilled water. Even after the effect of the carbon dioxid on the separation of thyroxin was discovered, its explanation was, for many months, obscure.

4. *Effect of temperature during treatment of a solution with carbon dioxid.*—After it was found that carbon dioxid had a very important action which allowed thyroxin to be isolated in crystalline form, carbon dioxid was added to the various solutions, first in the cold, and then it was added to the solutions warmed to various temperatures up to

100°C. It was found that with the preparations which were contaminated with a large amount of impurities, the passing of carbon dioxide into a solution above 50 to 60°C. resulted in breaking off iodine. This was confirmed many times, and, although for a long time unexplained, the solutions were always cooled before treatment with carbon dioxide.

5. *Effect of different samples of desiccated thyroid.*—The fifth point is one beyond control, and was found to rest on the condition of the desiccated thyroid employed. The thyroxine content of different samples of desiccated thyroid varies as much as 400 per cent. It appears probable that bacterial or other decomposition so alters the proteins in some samples that it is impossible to separate any of the iodine compound.

These five factors finally became apparent after a consideration of all the results obtained over a course of two years' investigation. It is remarkable that all these factors were unconsciously controlled during the first purification, especially as it took many months to find out that there were so many separate and distinct influences at work causing the destruction of the compound.

The investigation of the chemical constituents of the thyroid was begun by the writer in September, 1910. The use of barium salts to effect a separation was tried in November, 1914, and thyroxine was first isolated in December, 1914. Although over 100 mg. were isolated at that time, it was not until February, 1916, that the effect of carbon dioxide was established and more of the substance was obtained. During the summer of 1916 several grams of thyroxine were separated, and by May, 1917, over 7 gm. were available for its chemical identification. The empirical and structural formulas were determined during the summer of 1917. In December, 1917, Mr. Osterberg succeeded in synthesizing a small amount of thyroxine. The synthesis was repeated and the structural formula confirmed in April, 1919. Up to the present time about 33 gm. of the compound have been separated from 6550 pounds of fresh thyroid material which has been made up almost entirely of hog thyroid (Fig. 198). The method may be briefly stated as follows:

The fresh thyroid glands are hydrolyzed in 5 per cent sodium hydroxide. The fats are removed by rendering the sodium soap insoluble, and the clear alkaline filtrate is cooled and acidified. The acid-insoluble constituents containing practically 100 per cent of the thyroxine present are filtered off. This material is redissolved in



sodium hydroxid and reprecipitated, using hydrochloric acid. The precipitate is now air-dried and is dissolved in 95 per cent alcohol. The excess hydrochloric acid which remains in the air-dried precipitate is neutralized with sodium hydroxid until it is almost neutral to moistened blue litmus paper. A heavy, black, tarry precipitate forms, which may be removed by filtration. The alcoholic filtrate is treated with barium hydroxid by adding a hot, very concentrated

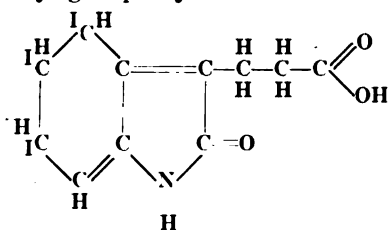


FIG. 198.—The three tanks in which 6550 pounds of hog thyroid glands were treated for the isolation of thyroxin.

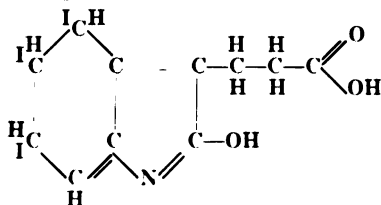
aqueous solution of the hydroxid to the alcohol, and refluxing. The treatment with barium removes some heavy dark impurities. A small amount of sodium hydroxid is added to the filtrate, and carbon dioxid is passed through the solution. The barium and sodium carbonate are removed by filtration, and the alcohol is distilled. The last traces of alcohol are removed by heating in an evaporating dish. The aqueous residue is now acidified with hydrochloric acid. The

precipitate is dissolved in alkaline alcohol, carbon dioxide is passed through the solution, the precipitated sodium carbonate is removed, and the alcohol is evaporated. The last traces of alcohol are removed by heating on a water bath and the solution is allowed to stand. The monosodium salt of thyroxine will separate at this point. The yield is not quantitative, and it must be further purified by dissolving in alkaline alcohol, passing in carbon dioxide, distilling the alcohol, and allowing the monosodium salt to crystallize a second time. This may then be precipitated from an alkaline alcoholic solution by the addition of acetic acid. Resolution in alkaline alcohol and precipitation with acetic acid for five or six times removes the impurities and will yield thyroxine containing the theoretical percentage of iodine. A considerable percentage of the total iodine present is carried down in the neutral alcohol solution by the barium, and another portion is held in solution when the monosodium salt separates, but it is not practicable to try to separate the thyroxine from these precipitates, as the yield is very small. Physiologically they possess the same activity as thyroxine when administered according to the iodine content.

After isolating about 7 gm. of thyroxine in the manner described, its empirical and structural formulas were determined and the substance was shown to be 4, 5, 6 tri-hydro-4, 5, 6 tri-iodo, -2 oxy, -beta indolpropionic acid. Thyroxine exists in three forms: (1) the keto form with the carbonyl group adjacent to the imino, (2) a tautomeric



enol form of this with an alpha hydroxy group and double-bonded nitrogen with no hydrogen attached to the imino, and (3) a form in



which there is an open-ring structure, the elements of water entering between the imino and the carbonyl with the formation of an amino and a carboxyl group. A consideration of the isolation of thyroxin after its structural formula had been determined explains the chemical reactions involved in the purification and isolation of the substance.

#### A CONSIDERATION OF THE REACTIONS INVOLVED IN THE ISOLATION OF THYROXIN

Thyroxin was first separated by following a method of treatment which was found to increase progressively its iodine content, and for the isolation of much of the material so far prepared this same method was followed without any light being thrown on the exact nature of the chemical reactions involved. The use of barium salts for the separation of thyroxin was first tried because of their ability to precipitate the dark-colored impurities from an alkaline solution of the hydrolyzed thyroid proteins. With the solutions of hydrolyzed proteins at first used, about 50 per cent of the total iodine could be precipitated by barium hydroxid. When the barium-soluble constituents were precipitated by an acid and redissolved in sodium hydroxid or carbonate, barium salts were found to precipitate some of the compounds which had previously been soluble in the presence of barium. This in time led to the discovery that the solubility of thyroxin in the presence of barium hydroxid was a test of its purity.

Partially purified thyroxin which is soluble in barium hydroxid is also soluble in sodium carbonate and in alcohol. Pure thyroxin is insoluble in these reagents. The process of purification rested essentially on the repeated treatments of the impure preparations of thyroxin with barium hydroxid and the recovery of the barium-soluble compounds by precipitation with an acid. The barium-insoluble constituents were recovered as sodium salts after decomposition with sodium sulfate and then precipitated with an acid.

After six or eight such barium treatments it was found that an increasing percentage of the total iodine was insoluble in barium hydroxid and finally it was shown that thyroxin could not be separated in crystal form from alcohol so long as it was soluble in barium hydroxid. Treatment with barium hydroxid influenced the separation of thyroxin in four different ways: (1) it effected a separation between the two forms of thyroxin, one barium-soluble,

the other barium-insoluble; (2) it caused the destruction of certain of the impurities which were present; (3) it precipitated certain impurities from the solution thereby effecting a separation; and (4) it carried down mechanically, when it was precipitated as barium sulfate, the dark-colored colloidal impurities which had almost identical solubilities as thyroxin itself and which were not removed by any other means.

The chain of events which led to the explanation of the reactions involved in the separation of thyroxin from the other compounds contained in the acid-insoluble products of the alkaline hydrolysis and the conversion of barium-soluble thyroxin into barium-insoluble thyroxin was as follows:

It was found that derivatives attached to the imino group render thyroxin soluble in alcohol. This was found true of the acetyl, the formyl, the ureide, the sulfate, and the hydrochlorid. It was also found that derivatives attached to the imino group do not form crystalline di-silver salts.

When thyroxin is partially purified, so that it contains from 30 to 50 per cent of iodine, it is soluble in alcohol and it does not form a crystalline silver salt. These reactions suggested that the difficulty in purification arose from the fact that some derivative was attached to the imino group, which rendered the compound soluble in alcohol and prevented its precipitation with silver. Since it had already been found that the sodium salts of the acetyl, the formyl, and other derivatives of the imino were readily thrown out of solution in crystalline form by increasing the amount of sodium hydroxid present, attempts were made to determine the group attached to the imino in partially purified thyroxin by precipitating its sodium salt with a high concentration of sodium hydroxid. Partially purified barium-soluble thyroxin containing about 40 per cent of iodine was therefore dissolved in sodium hydroxid, and a solution of 30 per cent sodium hydroxid was added to this. As had been hoped, the addition of the stronger alkali soon produced a cloudy precipitate which did not settle but remained suspended, due to the high specific gravity of the solution. This was centrifuged, the supernatant liquid contained most of the yellow impurities, and the precipitate remained as a firm felt on the bottom of the tube. It was dissolved in distilled water, sodium hydroxid was again added, the precipitate again formed, but this time it separated in more distinct particles and the solution was less

turbid. It was centrifugalized, the supernatant liquid was still yellow, but showed much less color than the first solution. The residue in the bottom of the tube was again dissolved in distilled water, sodium hydroxid was added, and this time the precipitate assumed a still different form, coming down in distinct separate particles, practically white, and the solution was almost colorless. These particles were examined under the microscope. They were the typical disodium salt of pure thyroxin itself, and not of a derivative. They were centrifugalized from the alkali, dissolved in alcohol, and precipitated by the addition of acetic acid, when they were recovered as pure crystalline thyroxin.

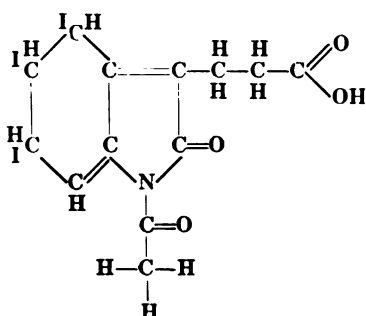
The substitution of sodium chlorid for sodium hydroxid permitted the solutions to be filtered instead of centrifugalized, and it was then found that sodium chlorid precipitated the disodium salt of thyroxin from an alkaline solution even better than sodium hydroxid. Although this sample of thyroxin had been completely soluble in barium hydroxid, it was now insoluble in such a solution. As this change in solubility could not have been brought about by the hydrolysis of a derivative attached to the imino group, it was apparent that solubility in barium hydroxid depends on the presence of certain impurities.

Investigation of the impurities which were separated from thyroxin by salting out the crystals from the alkaline solution showed that they are soluble in ether, that they are acidic in nature, and contain indole derivatives which give the pine-splinter reaction after fusion in caustic alkali. If pure crystalline thyroxin is dissolved in dilute sodium hydroxid and some of these indole derivatives are added to the solution, there appears to be an immediate reaction between thyroxin and these impurities which completely alters the chemical properties of thyroxin. The presence of these impurities renders thyroxin soluble in barium hydroxid, and instead of separating with sodium chlorid as the crystalline disodium salt, it is thrown out of solution as an oily tar.

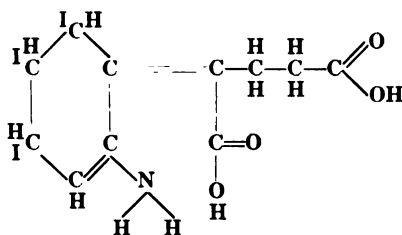
Since it was shown that this great alteration in the chemical properties of thyroxin could be brought about by the presence of certain indole derivatives of acidic nature, and since the change was not due to the hydrolysis of a derivative attached to the imino group, the first explanation was that the imino group was rendered more reactive by the presence of the impurities and that a salt forma-

tion occurred similar to the sulfate or hydrochlorid, the acidic group being attached to the imino nitrogen. However, it was difficult to explain all the reactions by such a change.

The first proof of the chemical reactions involved was obtained after preparation and analysis of the acetyl derivative. In the acetyl derivative of thyroxin, only one acid group is left which can react with a metal; therefore, a mono-metal derivative should be



obtained. Analysis of the silver salt of the acetyl showed that apparently two atoms of silver had added to the acetyl. The simplest explanation for this would be the opening of the pyrazole ring between the imino and carbonyl groups with the formation of the second free



carboxyl group. Further investigations showed that this is most probably true and that a similar opening of the ring occurs in thyroxin. The relation between the two forms is precisely the same as the relation between creatinin and creatin. The opening of the ring increases the acidic properties of thyroxin and renders it soluble in sodium carbonate, barium hydroxid, and alcohol. It prevents the formation of a crystalline insoluble di-silver salt and, in fact, all the changed properties of thyroxin are adequately explained by this reaction.

Analysis shows that the iodine content of barium-soluble thyroxin may be as high as 58 or even 60 per cent. This iodine content excludes

the possibility of any group being attached to the imino, having a higher molecular weight than formic acid. Furthermore, barium-soluble thyroxin can be changed and separated in pure crystalline form, insoluble in barium hydroxid, merely by allowing an aqueous sodium carbonate solution to stand several weeks. Under these conditions there is a slow closing of the ring with the formation of the mono-salt which is only slightly soluble. It seems most probable that the impurities present do not react in a stoichiometric relation with all the thyroxin, but that the presence of even a small percentage of the impurities introduces the factor of time and greatly delays the rate at which the ring closes.

Sufficient proof that a group is not attached to the imino group of partially purified thyroxin which is soluble in barium hydroxid, alcohol, and sodium carbonate is furnished by the fact that it is impossible to hydrolyze the acetyl from the imino group without disruption of the molecule. This also applies to all derivatives so far studied in which a group is attached to the nitrogen. Hydrolysis does not remove the group but destroys the integrity of the molecule. Therefore, the reactions occurring during purification cannot be the removal of a group attached to the imino. In the body it appears probable that thyroxin exists in the open-ring form with an amino and two carboxyl groups. The problem then in isolation is to establish conditions favorable for the closing of the pyrrole ring. The open-ring form of thyroxin will not crystallize and although it is but slightly soluble in acid, its solubility in carbonates, barium and calcium hydroxid, alcohol, and pyridin are in striking contrast to the closed-ring form which is insoluble in all these reagents. In the presence of certain impurities it appears very difficult, sometimes impossible, to close the ring and thereby separate thyroxin. The mere presence of these impurities is sufficient to open the ring if pure crystalline thyroxin is added to a solution of such impurities.

The exact nature of these impurities is still unknown, but they are among the hydrolyzed products of the thyroid proteins and contain the indole nucleus. Animo-acids from gelatin do not cause thyroxin to exist in the open-ring form. The difficulties encountered in separating the closed-ring form of thyroxin from any solution depends on the ratio between the amount of thyroxin present and the amount of impurities present. Thyroxin appears to carry down either chemically or mechanically these impurities so that solution in alkali

and precipitation with acid do not effect a separation. The best conditions so far found for the closing of the ring and the separation of thyroxin are obtained by solution of thyroxin in sodium carbonate. Under these conditions the ring slowly closes and the monosodium salt, which is only slightly soluble, deposits in crystalline form on the bottom of the flask.

#### SUMMARY

The chemical reactions involved in the five conditions, which influence the isolation of thyroxin, may be summarized as follows:

1. *Effect of temperature on precipitation with an acid.*—The chemical reactions involved in the acidification with an acid were very obscure until the acetyl derivative was prepared. It was found that when an acid suspension of the acetyl is neutralized with sodium hydroxid, at the neutral point, iodine breaks off from the acetyl derivative, and the liberation of iodine may be shown to be a matter of oxidation and reduction. Thyroxin is far less susceptible, and an acid suspension of thyroxin may be neutralized with an alkali without any such liberation of iodine occurring. When, however, an impure preparation of thyroxin is neutralized, the impurities appear to influence thyroxin in a manner similar to the addition of the acetyl group to the molecule, and at the proper hydrogen ion concentration, which is very nearly the neutral point, there is a reaction between the impurities and thyroxin resulting in a breaking off of iodine. Temperature greatly influences this reaction. If carried out in the cold solution, no destruction of thyroxin occurs.

Another effect of temperature during acidification is probably that of polymerization. Indole compounds polymerize very readily in the presence of acid. Thyroxin in pure state is slowly changed by boiling in strong acid, but when only partially purified the action of strong acid and heat brings about such a deep-seated alteration in the molecule that its physiologic activity is destroyed.

2. *Effect of heating the alkaline hydrolysis solution in the presence of metal.*—Thyroxin is very susceptible to reduction. An alkaline solution of thyroxin may be completely decomposed by heating with metallic zinc; the iodine is broken off from the molecule. Without doubt, the other metals, iron, copper, tin, lead, German silver, and, in fact, all metals except nickel, gold, silver, and platinum, react in the same manner, causing the destruction of thyroxin by reduction.



3. *Effect of carbon dioxid.*—There are two distinct actions produced by carbon dioxid. One is partial purification of thyroxin by precipitation from an alkaline solution. If an alkaline solution of partially purified thyroxin is treated with carbon dioxid until no further precipitation is produced, and the precipitate is removed by filtration, a large amount of material may be precipitated in the filtrate by the addition of a stronger acid. Thyroxin is precipitated by carbon dioxid more completely than, and at a point far in advance of, certain of the impurities. The effect of carbon dioxid as a precipitant depends on the ratio between the amount of thyroxin and the amount of impurities present. In the first solution of the acid-insoluble constituents of the hydrolyzed thyroid proteins, carbon dioxid will not precipitate any thyroxin. As the impurities are removed, the precipitation of thyroxin by carbon dioxid becomes more and more complete until in a solution of pure thyroxin the precipitation with carbon dioxid is quantitative. This influence of the impurities on the precipitation of thyroxin by carbon dioxid is one of the most striking examples of the effect of impurities on the chemical properties of thyroxin.

Another influence of carbon dioxid on the separation of thyroxin is more deep seated and was, at first, very difficult to explain. Thyroxin is soluble in sodium hydroxid with the formation of the disodium salt. If carbon dioxid is passed into such a solution, the hydroxy group gives up its sodium and exists in the free form. The carboxyl group, however, retains the sodium in the form of a mono-metal derivative. This is far less soluble than the di-metal derivative and readily crystallizes from the solution. When partially purified thyroxin, which exists in the open-ring form, is treated in this manner with sodium hydroxid and carbon dioxid, the optimum conditions are produced for the closing of the ring, and after standing for a considerable length of time the ring closes with the crystallization of the mono-metal salt of the closed-ring form of thyroxin.

4. *Effect of temperature during the treatment of a solution with carbon dioxid.*—This is closely related to, and is probably identical with, the effect of temperature on acidification of a solution with a mineral acid. The effect is the breaking off of iodine from the thyroxin molecule, and the mechanism is undoubtedly a reduction due to the presence of impurities and accelerated by the increase in temperature, the carbon dioxid functioning merely in producing the proper hydrogen ion concentration for this reaction to take place.

5. *Effect of different samples of desiccated thyroid.*—One of the most important reasons for the failure to separate thyroxin consistently was the variability of the samples of desiccated thyroid used. Analysis of the samples obtained at different times of the year shows that in the winter months, January, February, and March, the iodine content of the glands may be so low as to make the isolation impracticable. During the summer months the thyroxin content of the gland increases from 400 to 500 per cent and allows a much more liberal and much simpler purification of thyroxin. The amount of impurities present appears to be more nearly constant, so that in the winter months the problem is greatly complicated by having to deal with approximately the same amount of impurities and with a greatly diminished amount of thyroxin. It is significant that the real progress was made with the problem only when a satisfactory sample of desiccated thyroid was obtained, but this was demonstrated only after the completion of the work. Another influence, which undoubtedly is very important, not only in the isolation of the substance but in the consideration of the therapeutic value of any sample of desiccated thyroid, is the state of preservation of the thyroid proteins. Thyroxin has been shown to contain two carboxyl groups and one amino group, when existing in open-ring form, in which state it undoubtedly does exist in the thyroid proteins. Deamination and decarboxylation by bacteria are well known, and it seems highly probable that some samples of desiccated thyroid are without therapeutic value because of bacterial decomposition. Bacterial action could very readily result in deamination and decarboxylation of thyroxin, which would render the substance without physiologic activity although the iodine content of the material would not be altered.

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## THE PHYSIOLOGIC ACTION OF THYROXIN\*

E. C. KENDALL

In 1914 the physiologic action of the iodine compound occurring in the thyroid was in part described.<sup>2</sup> At this time it was stated that after the administration of this substance to dogs there was in every case a long delay before any physiologic effects were demonstrable. The action was described as follows:

"When injected subcutaneously in animals, there is at first no effect on either the pulse rate or the blood pressure. After from twenty-four to thirty-six hours the dog appears restless, has a slight increase in temperature, and a decided increase in pulse rate. If a series of injections is given on successive days, these symptoms are aggravated, and after two or three injections they are accompanied by a distinct tremor, loss of weight, and severe diarrhea. On the fourth or fifth day of injection the pulse rate is between 200 and 300, and all the other symptoms continue with increased severity."

While the investigation concerning the physiologic action of thyroxine is not yet completed, certain progress has been made which will be reported at this time. The iodine compound which in 1914 was tentatively named the "alpha iodine" compound, in order to differentiate it from the other iodine compounds occurring in the gland which were called "beta," has now been given the name "thyroxine."

Further investigation has confirmed the delay in the action of thyroxine in animals and in man, both in the normal condition and in myxedema. In a long series of patients suffering from myxedema who have been treated by intravenous injection of known amounts of thyroxine, Plummer has found that in all except two there was a very marked delay in the action of thyroxine. In these two patients there was a short-lived immediate response, but the prolonged action of thyroxine was noted as usual and the curve of the response after the first few hours was approximately the same as that given by the other patients.

\* Reprinted from *Endocrinology*, 1919, iii, 156-163.

Some of the early observations on the delayed action of thyroxin were obtained on goats. A series of eleven goats was injected daily with 14 mg. of thyroxin. The first goat died after eleven days and the rest followed at short intervals, all dying within thirty days. This shows that the long-continued presence of thyroxin in the animal organism is incompatible with life and it also suggests that death is not caused from the toxic action of the substance itself, but from secondary reactions. In order to bring this out more clearly another normal goat was injected with 230 mg. of thyroxin in a single injection. This amount was one and one-half times as much as was required to kill the first goat of the series, and yet the single injection of this relatively enormous dose produced almost no demonstrable effect, and the goat, even from the second day after the injection was, to all intents, normal.

Massive doses of thyroxin have also been given to dogs. Some were injected with thyroxin while they were receiving intravenous injections of sugar or of amino acids. In a few of these animals it was possible to demonstrate an immediate response to thyroxin, but this response very rapidly subsided and a long delay period followed before there were definite signs of the functioning of thyroxin.

Since the successive daily administration of thyroxin brings about death, and a single injection of enormous doses produces, in most instances, no demonstrable effect, we may conclude that the thyroxin molecule per se is not toxic to the animal organism. Although the intravenous injection of thyroxin produces no change in blood pressure, pulse rate, nervous manifestations, or any of the so-called hyperthyroid symptoms, the long-continued presence of thyroxin within the tissues of the body produces the picture of hyperthyroidism in its entirety, terminating in great emaciation and eventually in death. One factor, therefore, which would determine the reactivity of thyroxin would be the speed with which the tissues absorb thyroxin from the blood-stream. Even though thyroxin is circulated through the tissues of the body in the blood-stream, if the tissues refuse to absorb it from the blood it obviously could not produce its normal physiologic action. In order to determine whether or not the tissues remove thyroxin from the blood, 200 mg. were injected at once into the saphenous vein of a dog, and the bile and urine were saved for the next fifty hours. The bile and urine were analyzed for iodine and it was found that 43 per cent of the total iodine contained in the thyroxin

injected was excreted in the bile within fifty hours, and 13 per cent was excreted in the urine during the same time. This accounts for a large amount injected and, while the thyroid gland of this animal was not analyzed for iodine, it is highly probable that the remaining amount injected was removed from the blood-stream by the thyroid gland and there retained, making practically 100 per cent of the injected thyroxin unavailable for functioning within the tissues.

Marine and others have shown that the thyroid absorbs iodine when present in the blood and there can be little doubt that the gland absorbs and holds thyroxin, so that between the liver, the kidneys, and the thyroid gland, the excess of thyroxin is adequately cared for, and the tissues from a single injection do not take up enough thyroxin to result in a demonstrable physiologic response.

While no demonstrable physiologic response follows a single injection of thyroxin, there is no doubt that there is a physiologic response even to very small amounts. By the determination of the basal metabolic rate it may be shown that the myxedematous patient responds to exceedingly small amounts of thyroxin given in single injections. By "demonstrable response" is meant the increase in pulse rate and nervous manifestations with loss of weight, such as are observed when several administrations of thyroxin are given. The difference in the condition in the dog after one injection of thyroxin and after five injections is very striking, even though the weight of thyroxin given in the single injection is as great as the total amount used in the five injections.

Since the absence of thyroxin from the organism results in a lowered level of metabolic rate, and the administration of thyroxin determines the basal metabolic rate in the myxedematous patient, it seems highly probable that under normal conditions an equilibrium exists between the thyroxin in the thyroid gland, the amount in the blood-stream, and the amount in the tissues. It is probable that the amount in the tissues fluctuates according to the energy demands of the body, but that there is always an equilibrium seems highly probable. Under these conditions, if a large amount of thyroxin is injected into the blood-stream and nothing is done calling for an increased thyroxin content of the tissues, the tissues apparently are unable to absorb more thyroxin than their normal content and the excess is treated as a foreign substance and is promptly excreted in the bile. Some portion, however, is either excreted unchanged in the

urine or is broken down and thus excreted. If thyroxin is injected on several successive days the amount in the thyroid gland, the amount in the liver, and the amount in the blood eventually pass the normal limits for an appreciable period of time, with the result that the tissues are forced to absorb more than their normal content of thyroxin. When this process has started and secondary effects are brought into play the tissues are stimulated to such a height of activity that they, themselves, demand more thyroxin, and so the physiologic response is slowly built up. The full effect of the stepping-up process, however, is a matter of days, not a few hours. The tissues; once they have absorbed the thyroxin and begin to function at a higher rate of activity, in turn may affect the other ductless glands, especially the adrenal, as suggested by Cannon, and the increased activity of the adrenal, in turn, produces its train of effects.

Quantitative studies of thyroxin by Plummer have shown that not only is the appearance of physiologic effects of thyroxin delayed in man, but the duration of the effects is surprisingly long, and the maximum effect from a single injection of thyroxin in myxedematous patients is not reached until the tenth day. After reaching the maximum effect, thyroxin still continues to function for another eight to ten days, so that the length of time a single administration of thyroxin functions within the body is about three weeks.

What chemical reactions are so stimulated by thyroxin that life is incompatible are still unknown; but it is obvious that death is not due, in a strict sense, to the presence of thyroxin itself, but is due to the secondary effects which thyroxin brings into play.

One of the most important findings in connection with the physiologic activity of thyroxin has been the establishing of the quantitative relation between thyroxin and the basal metabolic rate. Plummer has shown that 1 mg. of thyroxin in an adult weighing approximately 150 pounds increases the metabolic rate 2 per cent. The curve of this response has been shown to be approximately a straight line between metabolic rates 30 per cent below normal to from 15 to 20 per cent above normal. This finding, coupled with the observation that all myxedematous patients tend to approach a uniform metabolic rate, which is about 40 per cent below normal, is extremely strong evidence in favor of the hypothesis that without the presence of thyroxin within the animal organism, rapid and large fluctuations in energy output would be impossible. Clinically this is substantiated by the

great difficulty the myxedematous patient manifests when endeavoring to walk upstairs or carry out any other muscular activity. Their range of fluctuation of energy output is limited. Their normal existence is at a rate in the neighborhood of 40 per cent below normal. However, by the administration of thyroxin this basal metabolic rate can be raised to any desired figure, and it can be so maintained over periods of time measured in years. These facts suggest that in the normal animal organism thyroxin is not fundamentally essential to life. The fundamental chemical reactions occur and life is maintained in the complete absence of thyroxin, but in this condition the flexibility of energy output is limited to a narrow range. The addition of the thyroid apparatus to the animal organism establishes not only a higher plane of basal energy output, but it supplies the mechanism which permits the maximum range in flexibility of energy output. The amount of thyroxin within the tissues is undoubtedly a physiologic constant, a figure as constant per weight of tissue as the normal number of red cells per cubic millimeter of blood. What determines this normal content of thyroxin is unknown. What maintains the content of thyroxin within the tissues is obviously the blood-stream. Some work has already been completed in this laboratory which has the objective of determining the thyroxin content of the blood and tissues. This may be done by determining the maximum iodine content of the blood and tissues. Whether or not the total iodine in the blood and tissues is 100 per cent in the form of thyroxin or 50 per cent cannot be shown, but the total amount of thyroxin could not be more than the amount indicated by the total iodine present in the tissues. The method for the determination of iodine which was published by the writer in 1914 has recently been further refined and perfected so that now one part of iodine in ten to twenty millions can be determined with a high degree of accuracy. By the use of this method it has been shown that the iodine content of the blood of animals is approximately 1.5 to 2 parts per ten millions; that is, 15 to 20 one-thousandths of 1 mg. per 100 c.c. The iodine content of the tissues is slightly higher, averaging 2.5 to 3 parts per ten millions; and the content of the liver is still a little higher, from 3.5 to 4 parts per ten millions. These figures must be amplified and confirmed by still more work, which is now being carried out, but they already indicate that there is an equilibrium existing between the amount of thyroxin in the blood, in the tissues, and in the liver.



If the presence of thyroxin within the tissues determines the metabolic activity of the tissues it is obvious that if there were no mechanism for varying the amount of thyroxin and if the tissues always contained enough thyroxin to permit of their maximum output of energy, the control of the energy output during periods of rest would be, to say the least, difficult. Whether or not the thyroxin content of the tissues diminishes after a period of great exertion, the thyroxin being carried back to the thyroid gland by means of the blood-stream and there held as a reservoir until further demanded, is still unknown.

This mechanism is at least indicated and is in part substantiated by the findings of the seasonal variation of the iodine in the thyroid gland. Seidell and Fenger have shown that during the winter months the thyroid glands of beef, sheep, and hogs all contain much less iodine than during the summer months. It is apparent that during the winter months more energy is required to maintain body temperature, and the low iodine content of the gland could be explained either by the fact that the thyroid gland has given up its supply of thyroxin to the tissues or by an actual wearing out of thyroxin due to the prolonged functioning of the substance in the tissues, so that during January, February, and March the amount left in the gland would be at a minimum. During the summer months, with less energy production in the animal, the amount of thyroxin demanded in the tissues is less. It reappears in the gland, either because its rate of production is greater than its rate of destruction, or because the amount in the tissues is returned to the gland and held there for use at some future time. The seasonal fluctuation of thyroxin in the gland is more satisfactorily explained on this basis than on the basis of varying iodine content of the food, and as it holds for beef, sheep, and hogs, it is suggestive that the mechanism of the variation is essentially due to the varied energy output of the animals during the cold and the hot months of the year.

In conclusion, the physiologic action of thyroxin is probably that of a catalyst which bears a quantitative relation to the production of energy within the tissues, and the curve representing this relation is a straight line; that is, the increase in energy production with an increasing amount of thyroxin is simply an additive one. The substance appears to function within the tissues, and there is an equilibrium between the amount in the tissues, the amount in the bloodstream, and its source of supply, the thyroid gland. The entire

absence of the substance from the body does not produce death, but merely a lowering of the level at which energy can be produced by the animal organism. In administering more than the normal amount of thyroxin to the animal organism there is a distinct lag in the absorption of the compound by the tissues and there is a rapid return to the normal content if the administration of the substance is stopped. The chemical reactions which are brought into play by the administration of thyroxin are probably not different from the fundamental chemical reactions occurring in its absence. As a catalyst it merely increases the rate at which these fundamental reactions are carried out. The thyroid apparatus apparently has been added to the animal organism in order to permit a greater range of flexibility of energy output than would exist without such a mechanism.

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# THE CHEMICAL IDENTIFICATION OF THYROXIN

## Second Paper\*

E. C. KENDALL AND A. E. OSTERBERG

Thyroxin is a white, highly crystalline substance, odorless, and tasteless. It may be separated from aqueous or alcoholic solutions in microscopic crystals which are not soluble in any organic solvent, except those which are strongly basic or acidic in nature. It is soluble in alcohol in the presence of mineral acid or an alkali metal hydroxid. It is stable toward heat, and its melting point is in the neighborhood of 250°C. Since it is odorless and colorless and is not easily affected by oxidation and reduction, its most important chemical and physical properties are concerned with the acidic and basic groups within the molecule. Thyroxin is a weak acid, but possesses basic properties in the presence of mineral acids.

In 1915, it was suggested that the organic nucleus in thyroxin is indol (2). Its solubility in alkali metal hydroxids, but not in carbonates, indicated that it was of phenolic nature, and its salt-forming power with acids was attributed to an imino group. After it was known that thyroxin contained about 60 per cent of iodine, and before the empirical and structural formulas were determined, the chemical properties of the molecule were best expressed by di-iodo-di-hydroxy-indol.

The first derivative of thyroxin, which helped to give an insight into its chemical structure, was the sulfate. Thyroxin which was precipitated from alkaline alcohol by acetic acid was found to contain 65 per cent of iodine. Thyroxin, precipitated by boiling an aqueous ammoniacal solution, also contained 65 per cent of iodine. Thyroxin,

\* Reprinted from Jour. Biol. Chem., 1919, xl. 263-334.



FIG. 199.—The hydrochlorid of thyroxin which separates in flat plates, rectangular, or star-shaped.



FIG. 200.—The free form of thyroxin separated as a sheaf of needles.

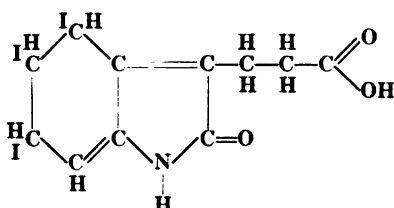
precipitated by adding sulfuric acid to an aqueous alkaline solution and boiling, was found to contain 60 per cent of iodine. The difference in iodine content was shown to be due to the formation of a salt with sulfuric acid, and by estimating the molecular weight of thyroxine from the molecular weight of sulfuric acid, it was found to be 585. With hydrochloric acid substituted for sulfuric, an iodine content, slightly higher than theoretical, indicated that the hydrochloride was hydrolyzed to some extent. Thyroxine in free form precipitates as needles, but the hydrochloride separates in flat, rectangular, and star-shaped plates. Examination of the crystals of the hydrochloride, which contained more iodine than theoretical, showed both the free form and the hydrochloride. The sulfate of thyroxine does not hydrolyze with water so readily as the hydrochloride (Figs. 199 and 200).

Ultimate analysis of thyroxine gave the percentages of carbon, hydrogen, oxygen, nitrogen, and iodine, and from these and the molecular weight of determination of 585 the empirical formula was shown to be  $C_{11}H_{10}O_3NI_3$ . In constructing the structural formula we were guided by the following:

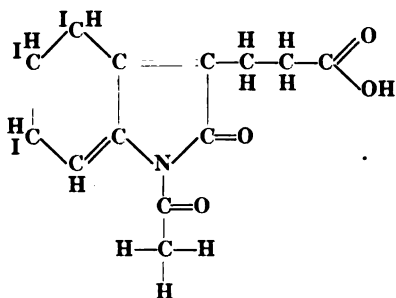
1. *Acidic properties.*—Thyroxine is readily soluble in sodium, ammonium, and potassium hydroxide, and is insoluble in sodium, ammonium, and potassium carbonate as ordinarily tested. It is soluble in aqueous sodium and potassium carbonate, however, if very little carbonate is added and the solution boiled. It is precipitated by carbon dioxide from an alkaline solution. The empirical formula and these acidic properties, therefore, suggest the presence of one carboxyl group, which has very weak acidic properties, and a hydroxy group.

2. *Basic properties.*—Thyroxine forms salts with mineral acids, but not with weak organic acids. This, together with the fact that thyroxine forms a ureide with cyanic acid, is evidence for the presence of an imino group. The identification of the indol nucleus by the pine-splinter reaction after alkaline fusion was evidence that the imino group was present as in indol. Accepting the presence of the indol nucleus, there remained three extra carbon atoms, a carboxyl group, a hydroxy group, three atoms of iodine, and three extra hydrogen atoms, whose positions in the molecule were to be determined. Since tautomerism is common in the indol group, it seemed probable that the position of the hydroxy group was adjacent to the imino, and that the three carbon atoms including the terminal carboxyl were

attached to No. 3 position\* of the indol nucleus. This structural formula, approximating that of tryptophane, satisfied all that was known concerning the chemical properties of the molecule except the position of the three iodine atoms and the three extra hydrogen atoms. As no special difference was demonstrable between the reactivity of the three atoms of iodine, it seemed most probable that they were all attached to the benzene ring, and as three extra hydrogen atoms would be required, if the iodine was added to, and not substituted for, hydrogen on the ring, they also were placed on the benzene ring. This formula is a tetra-hydro derivative of indol, the three atoms of iodine being substituted for three of hydrogen on the reduced benzene ring.



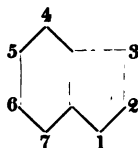
Structural formula of thyroxin: 4, 5, 6 tri-hydro- 4, 5, 6 tri-iodo- 2 oxy-beta-indol-propionic acid.



In proving the formula the first derivatives were those involving the imino groups. By the addition of acetic anhydrid to a slightly

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\* In this paper the positions in the indole nucleus will be referred to as follows:



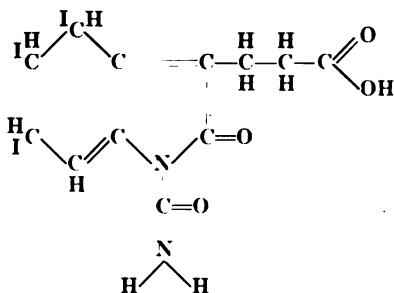
alkaline, alcoholic solution of thyroxin, the hydrogen of the imino is replaced with acetyl and the acetyl derivative may be separated in crystalline form by the addition of sulfuric acid and water and the removal of the alcohol by boiling under diminished pressure. The sulfate of the acetyl of thyroxin is thus formed. This is dissolved in a small amount of alcohol and when added to boiling water the acetyl



FIG. 201.—The crystal form of the acetyl derivative of thyroxin.

of thyroxin separates in pure form (Fig. 201). The melting point of the acetyl is slightly lower than that of thyroxin, it crystallizes in the form of needles more curved and much shorter than those of thyroxin, and although thyroxin is insoluble in all organic solvents the acetyl is readily soluble in alcohol, ether, ethyl-acetate, and dilute aqueous ammonia and pyridin. The close approximation, by analysis, of the theoretical percentage of iodine in the acetyl, 60.77, corroborates the molecular weight of 585.

Another derivative of the imino group which is easily formed is the ureid.



This is made by the addition of a salt of thyroxin, either the sodium or zinc salt, to acetic acid to which potassium cyanate has already been



FIG. 202.—The crystal form of the ureid derivative of thyroxin.

added. Cyanic acid reacts with thyroxin with the formation of the ureid. It separates from boiling water in curved needle form and has very closely the same solubilities as the acetyl (Fig. 202). Analysis of the ureid shows the percentage of iodine to agree with the theoret-



ical, 60.67. This is a third confirmation of the molecular weight 585. Although thyroxin forms a stable salt with sulfuric acid which is not hydrolyzed by boiling in dilute sulfuric acid, the addition of the acetyl of ureid groups to the imino increases the acidic properties of the imino, and these derivatives do not form stable salts with sulfuric acid except at low temperatures. Boiling the sulfate in dilute sulfuric acid causes a complete hydrolysis and separation of the acetyl or ureid in free form. The presence of the imino group in thyroxin is established by identification of the indol nucleus, the formation of the acetyl and ureid derivatives, and by the power to form salts with mineral acids.

The evidence for the carboxyl and hydroxy groups is as follows: Thyroxin is extremely insoluble in aqueous solutions of all acids, including carbonic. It is very easily soluble in sodium potassium and ammonium hydroxid, but the weakness of the acidic groups on the molecule is shown by the fact that boiling water alone causes a complete hydrolysis of the ammonium salt and free thyroxin may be precipitated in crystalline form by boiling an aqueous or alcoholic solution of its ammonium salt. Dilute solutions of sodium and potassium carbonate will dissolve only a small amount of thyroxin in the cold, but it is soluble in very dilute solutions of sodium and potassium carbonate at 100°C. However, on cooling such a solution, a mono-metal salt of thyroxin separates in crystalline form. If an excess of carbonate is present at first, the mono-salt of thyroxin is so insoluble in the presence of the excess sodium or potassium carbonate that most of the thyroxin being tested remains insoluble. The addition of a very slight amount of sodium or potassium hydroxid to a solution containing a suspension of thyroxin in the presence of sodium or potassium carbonate immediately carries the thyroxin into solution. These reactions suggest that there are present in thyroxin both carboxyl and hydroxy groups. The carboxyl group reacts with carbonates but the resulting mono-salt is so slightly soluble that the presence of excess carbonate forces the mono-salt out of solution. The hydroxy group in the presence of carbonates alone does not react, but the addition of hydroxid to such a solution forms a metal salt with the hydroxy group and the di-metal salt is readily soluble.

Still further evidence for this action is found in the barium salt. Barium chlorid added to a sodium hydroxid solution of thyroxin precipitates thyroxin in needle crystals, usually twined, or in sheaves

or bundles. If this is filtered off it is found to be slightly soluble in boiling water. On cooling and with the addition of a soluble barium salt to the solution, the barium salt of thyroxin recrystallizes quantitatively. If red litmus paper is dipped into a boiling aqueous suspension of the barium salt, the solution reacts neutral, but wherever the crystals of the barium salt come in contact with the paper the color of the indicator is changed to blue, showing that hydrolysis

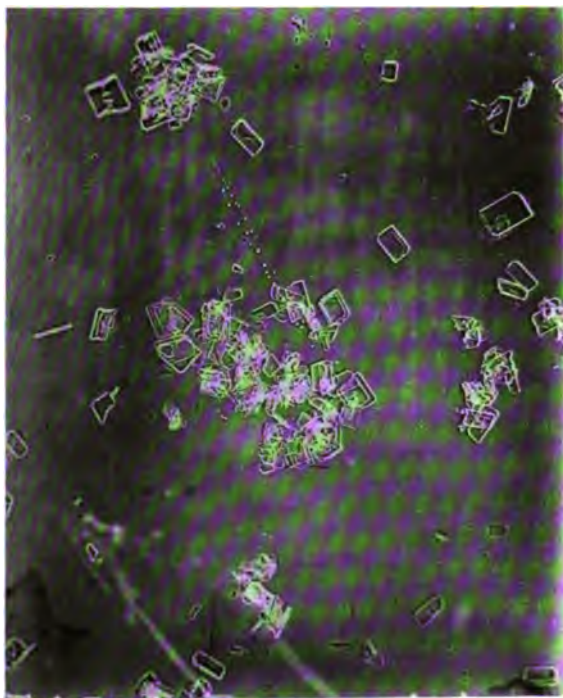


FIG. 203.—The mono-potassium salt of thyroxin which separates in small flat plates, rectangular, or square.

of the barium salt has occurred. If sodium hydroxid is added to an aqueous suspension of the barium salt of thyroxin the barium salt is dissolved and becomes almost as soluble as the sodium salt. This behavior is explained by the fact that the second hydroxyl group of barium hydroxid is not sufficiently strong to form a soluble salt with the hydroxy group of thyroxin. In the presence of boiling water the hydroxy group of thyroxin and one hydroxy group of barium exist in free form, barium forming a salt only with the carboxyl

group of thyroxin. Both hydroxy and carboxyl groups are slowly hydrolyzed by prolonged boiling of the barium salt in water.

The difference between the two acid groups is also shown in a sodium, potassium, or ammonium hydroxid solution of thyroxin. If carbon dioxid is bubbled through such a solution so as to produce sodium carbonate, but not bicarbonate, the hydroxy group is freed from metal and the mono-metal salt of thyroxin separates in flat



FIG. 204.—The mono-ammonium salt of thyroxin which separates in long blades.

crystals, oval, rectangular, or square. If an excess of carbon dioxid is passed through the solution, the carboxyl group also is freed and thyroxin will separate. The separation of the mono-sodium salt occurs at the point where the hydroxy group has been freed, but the carboxyl group is still in the form of a salt (Figs. 203 and 204).

While endeavoring to separate the metal salts for analysis the mono-sodium, potassium, and ammonium salts of thyroxin were prepared by dissolving thyroxin in strong solution of the hydroxids and passing carbon dioxid through these until the mono-metal salt separated. The crystals were filtered on a small Buchner funnel,

and washed with water. It was found that approximately 60 per cent of the amount of thyroxin taken was left on the funnel after drying in the supposed form of the mono-sodium, potassium, and ammonium salts. It was also found that if the salt was washed on the funnel with a 20 per cent solution of sodium or potassium chlorid, and not with water, the compound did not melt. When, however, the mono-salt was washed with water the sodium, potassium, and



FIG. 205.—The di-silver salt of thyroxin which separates in large, flat, rectangular and square plates, often occurring in sheaf form and twinned.

ammonium salts all had the same melting point,  $204^{\circ}$ . Since the mono-salt of thyroxin does not melt and the sodium, potassium, and ammonium salts, washed with water, all melt at exactly the same point, it seemed probable that the washing with water was sufficient to hydrolyze the very weak carboxyl, with the result that free thyroxin was left on the paper, the base being entirely washed away. In order to determine this the mono-ammonium salt was prepared as above, filtered, and washed with water and then analyzed for ammonia

by means of nesslerization. Nesslerization, although an exceedingly sensitive test for ammonia, failed to show the presence of even the faintest trace of ammonia in the supposed mono-ammonium salt of thyroxin. It was therefore evident that by washing the mono-sodium, ammonium, and potassium salts of thyroxin with water the weak carboxyl group can be completely hydrolyzed, and since the hydroxy group already was in the free form, the molecule existed with both carboxyl and hydroxy groups uncombined with metal.

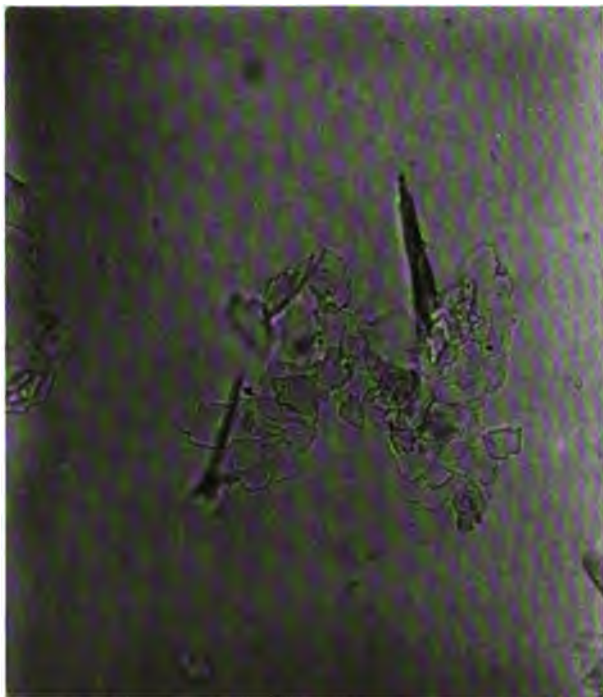


FIG. 206.—The di-potassium salt of thyroxin which separates in flat plates with rough, irregular edges.

Evidence that a di-metal derivative of thyroxin does form is furnished by the silver salt. Although a di-silver salt containing the theoretical amount of iodine has not been prepared, this salt has been made with so much silver present that it amounted to 92 per cent of the theoretical for the addition of two atoms of silver to the molecule. The reason why the theoretical di-silver salt cannot be prepared is undoubtedly due to the weakness of the hydroxy group (Fig. 205). When the di-silver salt, which is highly crystalline, is

washed in order to remove the excess of silver nitrate and ammonia which are used in its formation, the hydroxy group hydrolyzes to some extent, and the amount of silver remaining is slightly less than theoretical.

Di-basic salts of sodium, ammonium, and potassium are formed by dissolving thyroxin in the respective hydroxids, and adding a corresponding salt of the alkali, preferably the chlorid, until the di-alkali salt of thyroxin becomes insoluble and precipitates in crystal



FIG. 207.—The zinc salt of thyroxin which separates as long, flat blades in bundles and rosettes.

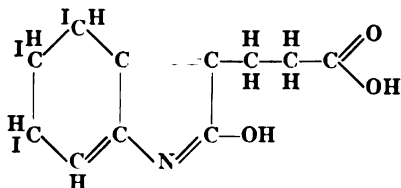
form (Fig. 206). Di-basic salts, which are only slightly soluble, have also been prepared with barium, calcium, magnesium, nickel, zinc, and copper (Fig. 207). Although all these salts may be made in beautifully crystalline and characteristic form, it is impossible to filter and separate them in a high state of purity by washing with water. Just as hydrolysis of the hydroxy group caused a lower silver content than theoretical with the silver salt, the hydrolysis of the hydroxy group with the barium salt shows a lower percentage

of iodine than theoretical. However, the weight of barium added is about twice that required for the mono-metal salt. With the less basic properties of calcium, magnesium, zinc, nickel, and copper even greater differences occur between the amount calculated for a di-metal salt and the amount found. But in every case since the amount of metal present nearly agreed with that required for a di-basic salt, the possibility that these are mono-basic salts is excluded. All salts of thyroxine which are insoluble in water such as the silver, copper, zinc, nickel, calcium, and magnesium are soluble in sodium hydroxide. The solubility is probably due to the same reactions that occur with the barium salt. The weak basic properties of the metals are insufficient to form soluble di-basic salts, but sodium hydroxide carries the salt into solution by adding to the hydroxy group of thyroxine.

Other evidence for the carboxyl and hydroxy group is furnished by the dimethyl ester. Methyl iodide added to an alcoholic suspension of the silver salt forms the dimethyl ester. This is soluble in alcohol but insoluble in water even in the presence of sodium hydroxide. By heating in dilute alcoholic sodium hydroxide, hydrolysis of the methyl ester of the carboxyl occurs and the oxymethyl derivative is obtained.

#### TAUTOMERIC FORMS OF THYROXINE

Thyroxine reacts in the presence of alkalis, forming di-basic salts, but differences between the two acidic groups indicate that one is a carboxyl and one a hydroxy group. When thyroxine exists in this form, which will be called the enol, the hydroxy group is adjacent to the nitrogen, but there is a double-bond between the nitrogen and the alpha carbon, and no hydrogen is attached to the nitrogen.



In acid solution thyroxine forms derivatives, which demonstrate the presence of an imino group, and exists in its tautomeric form, with imino carbonyl groups adjacent. This will be called the keto form.

When thyroxin was first isolated it was in the keto form and although it seemed probable that the hydrogen migrated in alkaline solution with a change from carbonyl to hydroxy groups, no quantitative data were available for proof of the hypothesis. When the mono-metal salts of sodium, ammonium, and potassium were prepared by freeing the hydroxy group in alkaline solution with carbon dioxide, it was found that by washing with water complete hydrolysis of the carboxyl



FIG. 208.—The crystals of the enol form of thyroxin.

also occurred. When the hydrolysis of the ammonium salt was carried out at  $100^{\circ}$  both acidic groups were not only freed but, in addition, the boiling water caused a change from the enol to the keto form. However, if the mono-metal salts are hydrolyzed with cold water the enol form is retained. There are many differences in the chemical properties of the enol and keto forms, but the most striking difference is in the melting point. The melting point of the enol form is  $204^{\circ}$ , that of the keto,  $250^{\circ}$ .



When the enol form of thyroxin was prepared by cold hydrolysis of its ammonium salt, it still retained the crystal form of this salt, but by dissolving the crystals in pyridin and adding water the enol form separated in its own characteristic crystal form (Fig. 208). The enol form of thyroxin separates in needle crystals which are much shorter than those of the keto form and always occur in rosettes or sheaf-like bundles. Crystallization does not alter the melting point.



FIG. 209.—The simultaneous crystallization of both enol and keto forms of thyroxin from an aqueous pyridine solution.

The keto form of thyroxin is by far the more stable and, unless precautions are observed, the enol form readily passes over into the keto. The most important factors influencing the change from enol to keto form are the presence of water and the hydrogen ion concentration. By adding water to a pyridin solution of the enol form, conditions may be produced in which both enol and keto forms simultaneously crystallize (Fig. 209). On long standing, even at room temperature, the enol form slowly changes over to the keto and the keto form alone separates. Since the chief chemical properties of thyroxin

are due to its basic and acidic groups, a brief summary of solubilities and reactions of the two tautomeric forms is of interest.

The enol form of thyroxin is much more soluble than the keto, and the solubility may be used as a test of the form in which thyroxin is present. For example, the keto form is insoluble in all organic solvents, such as all alcohols, ether, chloroform, ethyl acetate, acetone, carbon disulfid, quinolin, pyridin, anhydrous or aqueous, and anilin. The enol form is readily soluble in anhydrous or aqueous pyridin. Therefore, pyridin alone is not sufficiently basic to change the keto into the enol form, but when this change has been produced pyridin readily dissolves thyroxin. Since ammonium hydroxid in water, alcohol, or pyridin will change the keto form to the enol, but pyridin cannot produce this change, the hydroxyl ion concentration necessary for the conversion from one tautomeric form to the other lies between the basicity of dilute ammonium hydroxid and that of pyridin. Since the enol changes to the keto in a boiling aqueous pyridin solution, the acidity necessary for the tautomeric change in this direction lies between the narrow limits of the hydrogen ion concentration of a cold and a boiling aqueous solution of pyridin. The limits for the change in tautomeric form are at the same time the limits of solubility for thyroxin in alkaline solution. Thyroxin is soluble in enol form, in pyridin and quinolin, but any higher concentration of hydrogen ion causes the change to the keto form and limits the solubility of thyroxin in alkalis. Thyroxin in the keto form remains insoluble in all organic solvents with hydrogen ion concentrations equal to or less than that of glacial acetic acid. It is soluble in formic acid, but the subsequent addition of water causes thyroxin to separate again. Although acetic acid will not make thyroxin soluble in alcohol the addition of a mineral acid renders thyroxin readily soluble in alcohol. Solubility under these conditions is evidence for the formation of salts with the imino group.

The acid and basic properties of thyroxin therefore lie between these two limits: (1) The formation of salts with acids through the imino group of the keto form with formic acid, but not acetic, and (2) the formation of salts with alkalis through both the carboxyl and hydroxy groups with dilute ammonia, but not with pyridin. Lying between these two limits are the formation of mono-metal salts through the carboxyl alone in the presence of carbonates, but not bicarbonates, and finally the complete precipitation of thyroxin from

the alkali metal salts by carbonic acid or by hydrolysis with water in a boiling ammoniacal solution. The mono-metal salts of thyroxin are but slightly soluble in water but are easily soluble in alcohol. The solubility in alcohol is due to the fact that although only the carboxyl group is combined with metal, the molecule is in the enol and not the keto form.

The imino group of thyroxin reacts with all acids stronger than and including formic acid, but no acid salt of thyroxin is appreciably soluble in water, and even the sulfate which is the most soluble is only very slightly so. The great insolubility of the keto form of thyroxin is one of the most important factors permitting the isolation of the compound. The insolubility of thyroxin is also of importance in a consideration of its chemical properties. As soon as the proper conditions exist in any solution for the formation of the keto form of thyroxin, the reactive groups are thrown almost completely out of the sphere of reaction by the insolubility of the compound.

The keto form of thyroxin is soluble in organic solvents only when some acid is present which is capable of forming an acid salt with the imino group. Thyroxin may be conveniently purified by dissolving either in alkaline alcohol with the addition of acetic acid, or by dissolving in acid alcohol with the addition of sodium acetate. In the presence of acetic acid the imino group does not form a salt and thyroxin precipitates in needle form.

#### OPEN-RING FORM OF THYROXIN

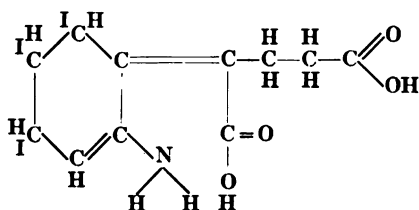
Since thyroxin in keto form is insoluble in bases weaker than ammonium hydroxid and is insoluble in alcohol in the presence of acids weaker than formic, there is a wide range of hydrogen ion concentration in which pure thyroxin is insoluble. These limits of solubility, however, apply only to pure thyroxin in aqueous and alcoholic solutions. In the presence of certain substances, changes in the acid and basic groups occur and the solubilities of thyroxin are materially altered and extended. In the presence of the products resulting from alkaline hydrolysis of the thyroid proteins the solubility of thyroxin is so greatly altered that it is completely soluble in carbonic acid, and even acetic acid produces an incomplete precipitation. Hydrochloric and sulfuric acids precipitate thyroxin under these conditions, but in excess they redissolve a considerable percentage of

the total amount present. The increased solubility in acids indicates an increase in the strength of the basic groups of the thyroxin molecule. Although pure thyroxin is practically insoluble in pyridin, sodium carbonate, barium hydroxid, and alcohol, partially purified thyroxin is readily soluble in the presence of all these reagents. The increased solubility in weak alkalies indicates an increase in the strength of the acidic groups in the thyroxin molecule. These changes in the chemical properties of thyroxin are most marked during the early stages of purification while there is a large percentage of impurities present, but that the alteration is due entirely to the impurities is disproved by the fact that both increased acidic and basic properties persist even after the removal of all but a trace of the impurities. Furthermore, the addition of certain substances to a solution of pure thyroxin brings about a similar increase in both basic and acidic properties. The solubility of partially purified thyroxin in weak alkalies is in such striking contrast to the solubility of pure thyroxin that it cannot be explained except by a change in the structure of the molecule other than the two tautomeric forms described above. The exact nature of this change was suggested by a study of the acetyl.

In all derivatives of thyroxin involving the hydrogen of the imino group, it is impossible to make the enol form, as the hydroxy group cannot exist. Because of the absence of the hydroxy group these derivatives should form mono-basic salts through the carboxyl group alone, they should be more insoluble in alkalies, and should form insoluble barium and silver salts. Since acid salts of the imino are soluble in alcohol, acetic acid, and ethyl acetate, it seemed probable that derivatives attached to the imino would also make the molecule soluble in these reagents. After the acetyl and ureid were prepared in pure form they were found to be easily soluble in alcohol, acetic acid, and ethyl acetate, but instead of being less soluble in alkalies, the acetyl was more soluble and could be held in solution with as weak a base as pyridin alone.

The acetyl was not only more soluble in weak organic bases but it also formed a silver salt which was completely soluble in dilute ammonium hydroxid. The silver salt of thyroxin will separate from strong ammonium hydroxid, but the silver salt of the acetyl is so soluble that it is impossible to prepare it in the presence of ammonia. By dissolving the acetyl in pyridin, however, the addition of silver nitrate produces a voluminous precipitate which may be washed

dried, and analyzed. When this was done it was found that the acetyl had formed a di-basic salt with silver. The formation of a di-basic salt by the acetyl indicated the presence within the molecule of another acidic group other than the terminal carboxyl. The simplest change by which a carboxyl group could be formed would be by introduction of a molecule of water between the imino and carbonyl groups, changing the imino carbonyl groups to amino carboxyl groups, and in the case of the acetyl the amino group is combined with one acetyl radical.



The presence of the acetyl radical in place of the imino hydrogen prevents the tautomeric change to the enol form, but in place of this, the ring opens even in the presence of weak organic bases. The acetyl attached to the amino group, however, does not prevent the closure of the ring, and if an alkaline solution of the acetyl, which is present in the open-ring form, is added to a dilute mineral acid at  $100^{\circ}$ , the ring closes and the acetyl separates in crystalline form. In addition to the di-silver salt of the acetyl, the zinc salt has been made, and di-basic sodium, ammonium, and potassium salts of the open-ring form of the acetyl may be prepared by dissolving in the respective hydroxids and adding a corresponding salt, the chlorid or acetate, until the salt of the acetyl becomes insoluble (Figs. 210 to 213). If sodium hydroxid and sodium acetate are used, very large, flat, jagged plates result; with sodium hydroxid and sodium chlorid short needle crystals are formed.

Barium and calcium salts of the acetyl can also be formed by the addition of barium or calcium chlorid to a solution of the acetyl in dilute sodium hydroxid or pyridin. An excess of pyridin dissolves the salt.

After the physical and chemical properties of the acetyl derivative had been established, it was found that a most striking resemblance existed between partially purified thyroxin and the acetyl.



**FIG. 210.**—The di-sodium salt of the acetyl derivative separated from a sodium chlorid solution.



**FIG. 211.**—The di-sodium salt of the acetyl derivative separated from a sodium acetate solution.



FIG. 212.—The di-potassium salt of the acetyl derivative.

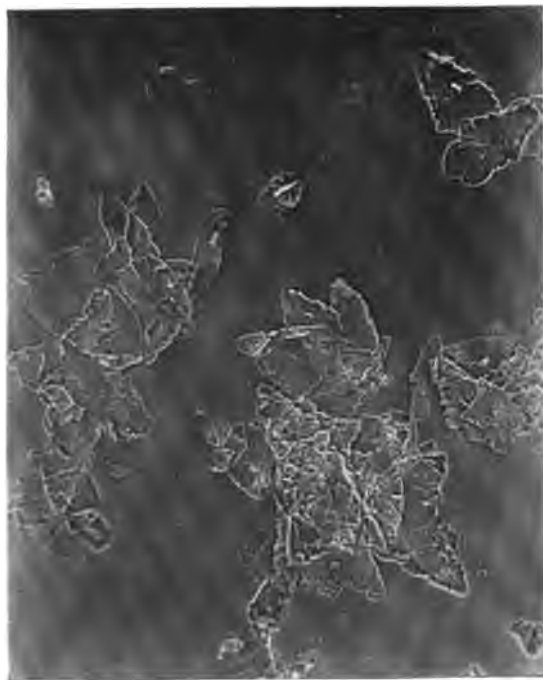


FIG. 213.—The di-potassium salt of the ureid of thyroxine which separates in a manner similar to the di-potassium salt of the acetyl derivative.

The acetyl differs from thyroxin in having wider limits of solubility in weak bases, and the greatest difference between partially purified and pure thyroxin is the solubility of the former in the weaker alkalies, sodium carbonate, barium hydroxid, pyridin, and in alcohol. These reactions suggested that in partially purified thyroxin the structure of the molecule is similar to that of the acetyl. But the possibility that an acid radical was attached to the imino group, as in the acetyl, could be excluded by the fact that the thyroxin could be separated in keto form. The increase in both acidic and basic properties, its close resemblance in chemical reactions to the acetyl, and the fact that it could be separated in the keto form suggest that in partially purified thyroxin the molecule is present neither in the keto nor enol forms, but that the pyrrol ring exists in open form, the elements of water entering between the carbonyl and imino groups.

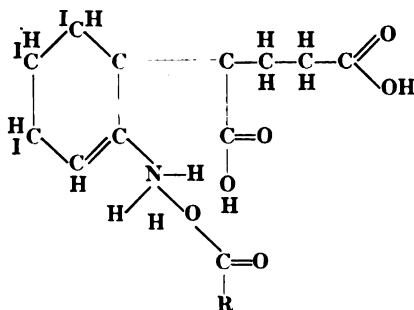
This structure of the molecule of thyroxin will be called the open-ring form. The open-ring form of indol derivatives containing an alpha carbonyl group is of common occurrence, but thyroxin is perhaps unique in the great ease with which the ring opens and the great difficulty with which the ring closes in the presence of certain substances.

Although the open-ring structure of thyroxin was first suggested by a study of the acetyl, further investigation has amply confirmed this hypothesis and brought to light the delicately balanced reactions, which, in all probability, are involved when the substance functions physiologically. These reactions are concerned with the opening and closing of the ring and the formation of salts with acids by the amino and imino groups. When sulfuric acid is added to a slightly alkaline alcoholic solution of thyroxin and the alcohol is distilled, the sulfate of thyroxin separates, the sulfate radical being attached to the imino group. However, if sulfuric acid is added to an alkaline aqueous solution of thyroxin, the resulting precipitate is not the imino sulfate of thyroxin. Analysis of this precipitate for its iodine content showed that thyroxin had not precipitated in free form but contained one equivalent of acid. Further investigation showed that thyroxin precipitates with one equivalent of acid, not only with sulfuric but with weak organic acids and that even carbonic acid adds to thyroxin when carbon dioxide is passed through an alkaline solution. The sulfate, chlorid, phosphate, trichloracetate, oxalate, formate, acetate, and carbonate of thyroxin have been prepared. All these salts are soluble in alcohol and have melting points which are strangely similar, all of them

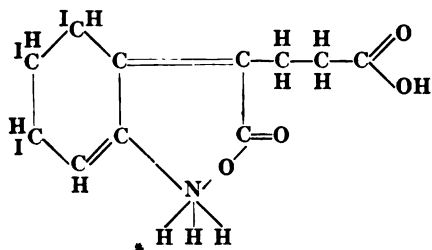


melting at about  $204^{\circ}$ . Although the imino group of thyroxin in keto form is so feebly basic that in hot dilute hydrochloric solution the acid radical is hydrolyzed and the imino group exists in free form, when the enol form of thyroxin is precipitated by an acid, an equivalent of acid is contained in the precipitate attached to thyroxin. If any of these salts, prepared by acidifying an alkaline solution of thyroxin, are moved from solution, suspended in distilled water, and boiled, a change occurs, and thyroxin precipitates in long, bundle blades. These blades differ from the keto form of thyroxin in being soluble in alcohol and having a melting point of  $225^{\circ}$ . If instead of suspending the acid salts in distilled water, they are added to a dilute solution of hydrochloric or sulfuric acid and are then boiled, the keto form of thyroxin separates. These reactions are interpreted as follows:

When an acid is added to the enol form of thyroxin, the nitrogen becomes pentad and the acid radical adds to the nitrogen. In aqueous solution the pyrrol ring is no longer stable and the elements of water add between the pentad nitrogen and the carbonyl group, forming a carboxyl group and an acid salt of the amino group. In cold water solution this reaction occurs not only with sulfuric and strong organic acids, such as trichloroacetic and oxalic, but even carbonic acid is capable of adding to the amino group.



When the amino salt is suspended in distilled water and boiled, the amino group is hydrolyzed free from the acid, and the carboxyl group which is adjacent to the amino group forms a salt with the amino group. The compound then exists in an amino carboxyl salt form, the acid used in precipitating thyroxin having been expelled from the amino group by hydrolysis with water.



This form of thyroxine differs from both the keto and enol forms in having the addition of the elements of water. It has a melting point of  $225^{\circ}$  and is soluble in alcohol (Fig. 214). It is converted into the

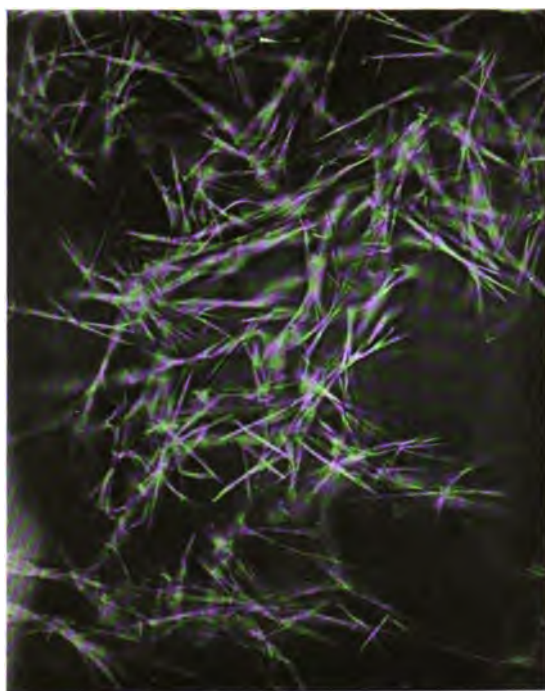


FIG. 214.—Crystals of thyroxine in the amino carboxyl form.

keto form very easily; merely solution in alcohol is sufficient to expel the water, and the keto form of thyroxine then separates. It is impossible to separate the amino carboxyl salt form of thyroxine from solutions containing a high percentage of alcohol. Further investigation showed that this is also true of pyridin and other organic solvents. It is necessary to have water present in order to force the opening of the pyrrol ring.

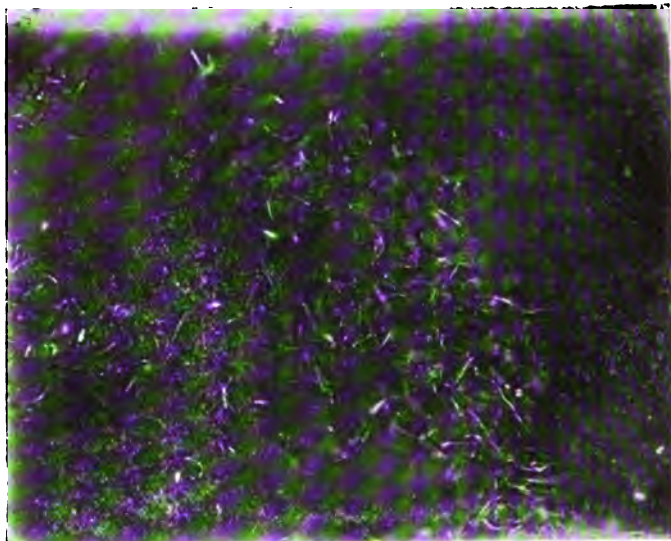


FIG. 215.—Crystals of the amino carbonate of thyroxine.

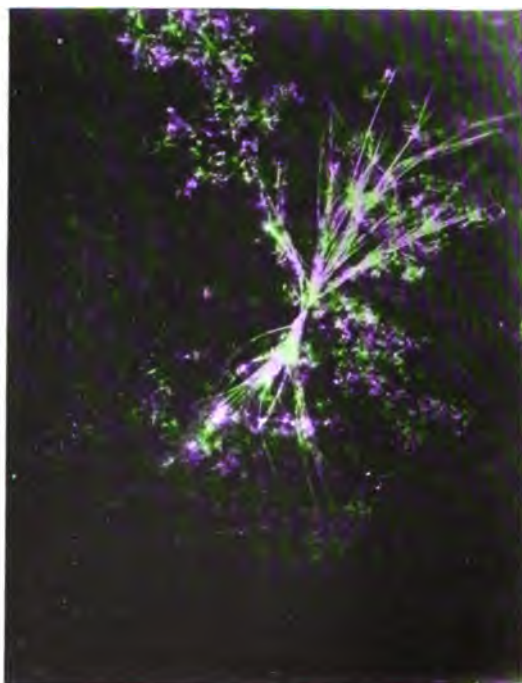


FIG. 216.—A mixture of the crystals of the amino formate changing into the amino carboxyl salt form of thyroxine. The long needles are the amino carboxyl crystals.

If any acid salt of the amino group of the open-ring form of thyroxin is suspended in distilled water and boiled, the carboxyl group in thyroxin, which is adjacent to the amino, will displace the acid radical attached to the amino, and the amino carboxyl salt form of thyroxin results. If the acid radical which is added to the amino is sufficiently strong and an excess of the acid is present, the ring does not remain open, but the elements of water are expelled and the strong acid radical

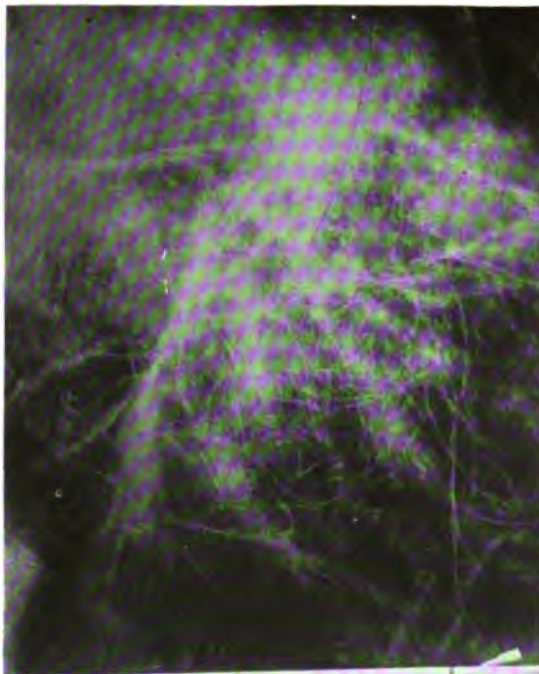


FIG. 217.—A mixture of amino carboxyl crystals changing into the keto form of thyroxin. The long needles are crystals of the amino carboxyl form of thyroxin.

is either hydrolyzed from the imino group or remains attached as an acid salt of the imino group. The closing of the ring of an amino-acid salt is influenced by many factors, such as the amount of acid present, the strength of the acid, and the presence of organic solvents, such as pyridin or alcohol. Strong acids promptly close the ring, forming imino salts; weak acids are expelled from the amino, and the molecule exists in the amino carboxyl form. The presence of organic solvents such as alcohol results in the closing of the ring and the formation of imino salts with strong acids, or the displacement of

the acid with the separation of thyroxin in keto form. If an amino-acid salt of the open-ring form is washed free from all acid, suspended in neutral water, and boiled, the acid is promptly hydrolyzed from the amino group and the amino carboxyl salt form results, but in the absence of excess acid in solution this form of thyroxin is unstable at 100°C., water is rapidly expelled from the ring, and the keto form of thyroxin separates in very fine thread-like crystals. Under proper conditions all three forms may be present at the same time (Figs. 215 to 217).

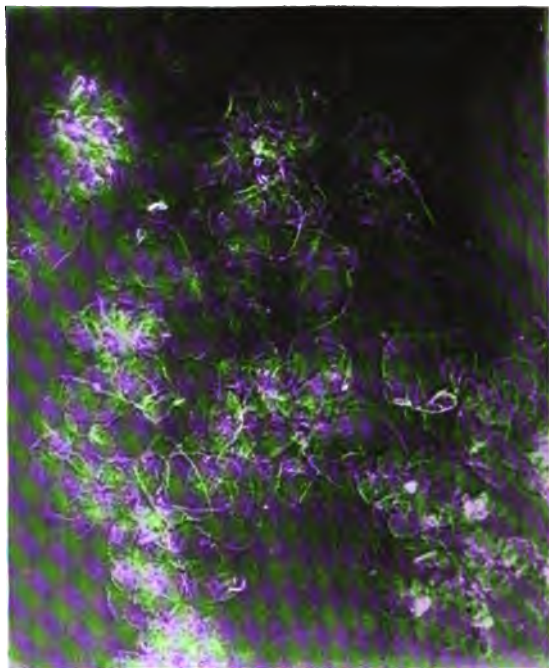


FIG. 218.—The imino sulfate of thyroxin separated from a hot solution

Since acids added to the enol form of thyroxin in aqueous solution cause an opening of the ring, the question arose as to whether the opening of the pyrrol ring is the primary action, or whether it is secondary to the existence of the nitrogen in the pentad form. That the opening of the ring occurs without passing through the enol form is shown by the formation of the amino sulfate directly from the imino sulfate (Figs. 218 and 219). When the imino sulfate is present in a small amount of alcohol and water is added, the ring opens and the

amino sulfate separates even though the molecule had existed in the keto form. The formation of amino salts from imino salts shows that the ring opens readily when the nitrogen is in the pentad state, but that the opening of the ring also occurs directly from the enol form in a solution slightly alkaline may also be shown. When the di-sodium salt of thyroxin is dissolved in cold water and ammonium chlorid is added to the solution, the sodium is hydrolyzed from hydroxy

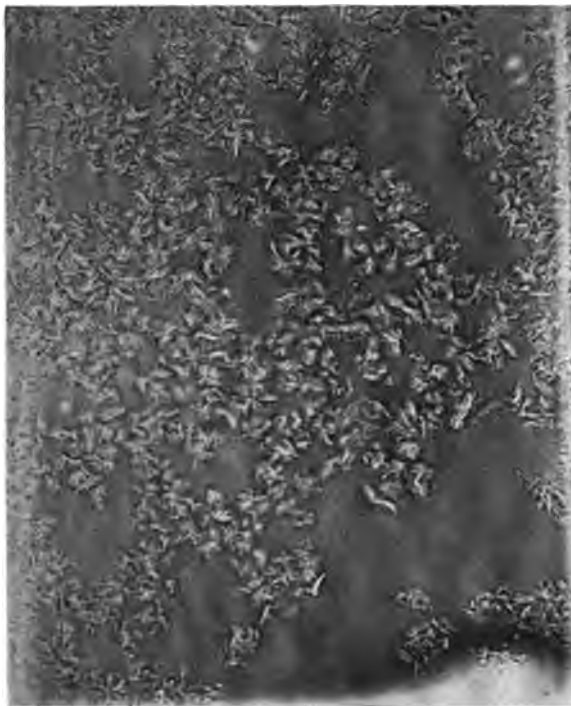


FIG. 219.—The amino sulfate of thyroxin formed from the imino sulfate of thyroxin by the addition of water to an alcoholic solution of imino sulfate.

and carboxyl groups, resulting in the precipitation of thyroxin in the enol form. If this suspension of the enol form is now boiled the crystal form changes into the typical amino carboxyl salt form, the melting point of which is  $225^{\circ}$ . The crystals are also readily soluble in alcohol, which excludes the possibility of their being in the keto form. A more direct evidence of the existence of thyroxin in opening form is obtained by dissolving the di-sodium salt in hot water and adding ammonium chlorid to this hot solution. Instead of thyroxin

separating in the enol form, it separates directly as the amino carboxyl salt form. The most important factor in this reaction is the presence of excess alkali. If much alkali is present, the molecule exists in the enol form and addition of ammonium chlorid will cause a separation of the mono-ammonium salt.

From these results it would appear that in acid alcohol solutions thyroxin exists in the keto form. In the presence of excess alkali in aqueous solution thyroxin exists in the enol form, but as the neutral point is reached from either direction there is a tendency for the ring to open. In a hot neutral solution the ring does open. In a cold neutral solution even carbonic acid will open the ring and add to the amino group.



FIG. 220.—The crystals of the amino hydrate form of thyroxin.

#### THE AMINO HYDRATE FORM OF THYROXIN

The pyrrol ring of thyroxin not only has a tendency to take up water between the imino and carbonyl groups and exist in amino carboxyl form, but the amino group is so strongly basic that in a

slightly alkaline solution the elements of water will add to the nitrogen forming the amino hydrate.

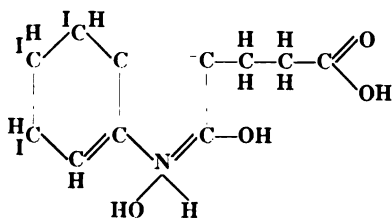


FIG. 221.—A mixture of enol and keto forms of thyroxine crystallizing simultaneously from the same solution.

This form of thyroxine is tautomeric with the amino carboxyl form. It is very readily prepared by heating an alkaline solution of thyroxine, removing the solution from the flame, and adding 10 per cent ammonium chlorid. The solution becomes turbid, and fine branching crystals separate (Fig. 220). The melting point of this form of thyroxine is  $216^{\circ}$ . If these crystals are suspended in distilled water containing a small amount of formic acid and the solution is boiled,



the crystals are changed into their tautomeric amino carboxyl form, whose melting point is  $225^{\circ}$  (Figs. 221 and 222).

One form of thyroxin changes into another so easily that enol and keto forms will crystallize simultaneously out of the same solution and amino-acid salt, amino carboxyl salt, and keto forms may all be present at the same time, one form changing into another as the boiling of the solution is continued. The ready change of thyroxin from one



FIG. 222.—A mixture of the crystals of the amino carboxyl form changing into the keto form. The small rosettes are crystals of thyroxin in the keto form.

form to another is explained by the great ease with which the pyrrol ring opens and the elements of water are added to the molecule. This reaction does not occur with indol or isatin and was not at first easily explained in the case of thyroxin. While engaged in the preparation of the intermediate products for the synthesis of thyroxin, our attention was drawn to the fact that the explanation of the peculiar properties of the imino group in the pyrrol ring of thyroxin is the presence of the hydro groups in the benzene ring. Anilin is a feeble base and the imino group in indol is still more feebly basic.

Hexa-hydro-anilin has such a strongly basic amino group that it will combine with carbon dioxide from the air, and it has a very caustic action on the skin. It is the addition, therefore, of four hydro groups to the molecule that so modifies the nucleus, giving basic properties to the imino group of the pyrrol ring of thyroxin. Speculation as to the properties of the compound in which the three iodines are replaced by three hydrogens may be deferred until the substance is prepared synthetically, but that the imino group of the pyrrol ring will be still more basic in this compound would naturally follow from the general law that addition of halogen to the benzene ring renders the ring more acidic. The position and reason for the three extra hydrogens in thyroxin were unknown and were very puzzling until the reactions of the compound involving the amino and imino groups caused the necessity of explaining this action by some modification of the indol nucleus. Since the introduction of the six hydro groups in anilin greatly increases the basicity of the amino group, the addition of four hydro groups to the indol nucleus of thyroxin is an adequate explanation of the increased basicity of its amino group. The instability of the pyrrol ring of thyroxin in contrast to that of indol and other unreduced derivatives of pyrrol is due to the increased basic properties of the nitrogen in thyroxin. This point is well illustrated in the stability of the amino carboxyl form. In neutral solution the nitrogen tends to become triad, the pyrrol ring is more stable than the amino carboxyl salt, and thyroxin separates in keto form. If a slight amount of acid is present, the nitrogen remains in the pentad state and the amino carboxyl form is so stable that it is impossible to expel water from the molecule and make the keto form. The difference in the basicity of the nitrogen when changing from the open- to the closed-ring forms is probably involved when thyroxin functions physiologically. But the unique chemical properties of thyroxin are also due in large measure to the carbonyl group adjacent to the imino, and the reactivity of the substance *in vivo* and *in vitro* is due to the presence of this oxy group in the indol nucleus. It was for this reason that the compound was named thyro-oxy-indol or thyroxin.

After it was found that thyroxin forms amino salts with feeble carboxyl groups, it was of especial interest to form the amino salt of thyroxin with glycine. Reserving a study of the reaction between thyroxin and the amino-acids for a further communication, merely the

formation of an amino-acid salt between thyroxin and glycin will be reported in this paper.

Since acid added to the enol form of thyroxin results in the formation of an amino salt, it seemed probable that at least a portion of the nitrogen of thyroxin should react as amino nitrogen with nitrous acid when the molecule existed in the amino-acid salt form. This was tried and it was found that when an alkaline aqueous solution of thyroxin was added to a Van Slyke amino-acid apparatus, approximately 70 per cent of the total nitrogen present was liberated as amino nitrogen. When the keto form of thyroxin was used, no nitrogen was evolved. When the amino carboxyl form of thyroxin is added to nitrous acid, about 15 per cent of its total nitrogen is evolved as amino nitrogen. The reason that a quantitative evolution of amino nitrogen does not occur with the last mentioned form in three minutes is because the crystals are insoluble and the reaction takes place at a very slow rate.

When nitrous acid is added to an alcoholic solution or to an aqueous suspension of thyroxin in the presence of hydrochloric acid, a yellow color is produced. Upon the addition of ammonia this is changed to a deep red which in dilute solution is pink. This color reaction is convenient for a rough qualitative test for thyroxin. However, if acetic or sulfuric acid is used in place of hydrochloric, a fainter yellow color is produced, and the addition of ammonia gives a yellowish orange instead of a red color.

During the purification of thyroxin, the presence of colloidal impurities is sufficient to cause the opening of the ring and also to prevent the closing of the ring. When an alkaline solution of thyroxin is acidified the precipitate carries down many of the impurities present as salts of the amino group and hence no quantitative separation can be effected by precipitation with an acid. The chief problem in the isolation of thyroxin is to close the ring in the presence of the impurities, and thereby produce chemical properties specific to the thyroxin molecule, which permit of a separation. This difficulty in closing the open-ring form of thyroxin is well illustrated in the course of its purification. Approximately 50 per cent of the iodine content in the early steps of the separation of thyroxin is soluble in barium hydroxid. This barium-soluble portion may be hydrolyzed by heating with barium hydroxid for many hours, precipitated with acid, given another treatment with barium hydroxid, and this process continued as

many as seven or eight times without rendering thyroxin insoluble in barium hydroxid. This treatment, however, slowly separates many of the impurities and the percentage of iodine in the dry material may reach as high as 58 per cent. Thyroxin in this open-ring form contains sufficient impurities to impart a distinctly yellow color, and it is readily soluble in sodium carbonate, barium hydroxid, pyridin, and alcohol. By chance such a preparation was dissolved in sodium carbonate solution and was allowed to stand seven weeks. At the end of that time a white residue had separated and settled to the bottom of the flask. Examination showed this to be the monosodium salt of thyroxin. Although the material was in the open-ring form when dissolved in the carbonate, on long standing the ring had closed and the compound thereby became insoluble in sodium carbonate.

The open-ring form of thyroxin cannot be precipitated from alcohol with acetic acid. The keto form of thyroxin is very nearly quantitatively precipitated from alcohol by acetic acid, but as long as impurities are present, an alcoholic solution of the open-ring form of thyroxin may be allowed to stand several weeks without the separation of any trace of thyroxin. If, however, an alcoholic solution of thyroxin is slowly evaporated on the water bath, the evaporation causes a partial separation. A yellow oily tar creeps up the inclined bottom of the evaporating dish and forms a ring as the alcohol evaporates. At the spot where the last trace of alcohol was left, a dry crusty material, which is almost white, shows the partial separation of thyroxin in the keto form. This property of thyroxin to separate from alcohol, even in the presence of impurities, is the reaction by which thyroxin was first isolated. The alcohol in this case was evaporated unintentionally, and, although the entire sample of thyroxin had been completely soluble in the alcohol, the slow evaporation and subsequent heating at 100° was sufficient to close the ring in a small percentage of the total amount with the result that it was insoluble on the addition of more alcohol. This method of separation is not of great value for the isolation of the compound. The best method so far determined for the closing of the ring is to dissolve thyroxin in alcohol containing sodium hydroxid, and pass carbon dioxid through the solution, freeing both hydroxy and carboxyl groups. Most of the sodium carbonate is insoluble and is removed by filtration. The alcohol is distilled, leaving an aqueous sodium carbonate solution of thyroxin,

but still in open-ring form. Allowing this to stand for several days will cause a separation of the mono-sodium salt in the enol form which may be purified by similar treatment.

#### OXIDATION AND REDUCTION OF THYROXIN

Quantitative oxidation and reduction experiments with thyroxin have not been carried out because of the amount of material which would be required in order to isolate the products. Thyroxin is more susceptible to reduction than to oxidation. Zinc in alkaline or acid solution breaks off iodine and appears to alter the organic nucleus. Thyroxin is reduced when heated in the presence of any metal in alkaline solution other than nickel, and the heavy metals, silver, gold, and platinum. Thyroxin is stable in the presence of mild oxidizing agents. Hydrogen peroxide produces no immediate effect and in a cold acid suspension the molecule will resist oxidation with potassium dichromate or iodic acid. Potassium permanganate or bromine in hot aqueous solution causes the breaking down of the molecule. Benedict's copper solution, for the determination of sugar, causes an oxidation of thyroxin in the presence of sodium hydroxide. In the presence of ammonium hydroxide alone, thyroxin is stable in Benedict's solution heated to boiling. Free iodine if added to an alkaline solution produces a precipitate and apparently brings about a deep-seated reaction within the molecule. In acetic acid or acid alcohol, iodine has very little, if any, effect on thyroxin even at the temperature of boiling acetic acid. Further investigation showed that, in the presence of iodine, thyroxin is stable in the keto form, but not in the enol form. The changes produced by oxidation with chlorine, bromine, and iodine have not been determined, but in alkaline solutions yellow tarry products are formed. Since the enol form of thyroxin is so much less stable than the keto, the weakness in the molecule appears to be in the linkage of the nitrogen, and the point of cleavage is probably between the nitrogen and the hydroxy groups. When the imino carbonyl groups are present, the molecule is much more resistant to oxidation by halogen.

Another point of weakness within the molecule exists in the benzene ring. The completely reduced benzene ring readily passes over into a six carbon, straight chain form. Hexo-hydrophenol may be readily oxidized to adipic acid by the action of dilute nitric acid. In thyroxin the benzene ring is in the tetra hydro form, and it is highly

probable that the one double bond which is present will break down with the formation of an open chain structure. A reaction similar to this is found in the oxidation of the tetra-hydro-benzene ring of sedanonic acid<sup>1</sup> to straight chain acids.

Due to the weakness of the linkages to the nitrogen in thyroxin, it is impossible to hydrolyze derivatives from the imino group. After the acetyl radical has been attached to the imino group, it cannot be hydrolyzed with sodium or potassium hydroxid. When treated with alkali, the compound precipitates as a di-metal salt, and is thrown out of solution. If sufficiently drastic action is applied to bring about the hydrolysis, disruption of the molecule occurs.

Thyroxin upon exposure to the sunlight in weak alkaline solution is very unstable. Within twenty-four hours the solution changes from colorless to a pink, or faint yellow, which deepens on standing to a brown color, depending on the amount of thyroxin present. Simultaneously with the discoloration a distinct aromatic odor is produced slightly resembling that of nicotine. Such a solution, when tested for iodine by means of starch in acid solution, shows that no iodine has been broken off in the free form. If, however, a small amount of potassium iodide is added, iodine is immediately liberated, which indicates that the iodine within the thyroxin molecule was not broken off either as hydriodic acid or as iodine, but in the form of hypo-iodous acid. On longer standing a test for free iodine is given without the addition of potassium iodide and the amount of hypo-iodous acid is much reduced. After several weeks no test for iodine or hypo-iodous acid is given, but all the iodine is found in the form of hydriodic acid. The reduction of the hypo-iodous acid to hydriodic acid is probably brought about by the hydro-indol nucleus. The finding that iodine is broken off from the thyroxin molecule in the form of hypo-iodous acid and not as hydriodic has direct bearing on the physiologic action of the molecule within the body.

#### THE ACETYL DERIVATIVE

With the acetyl, sunlight produces a similar reaction, but in this case the solution is found to contain both hypo-iodous acid and iodine. The acetyl derivative, therefore, is more susceptible to oxidation than thyroxin, and brings about a much more rapid reduction of the hypo-iodous acid to iodine and hydriodic acid.

So unstable is the acetyl under certain conditions that there is a spontaneous liberation of iodine from the molecule and the simultaneous oxidation of the organic nucleus, resulting in a change of color and the production of a yellow tarry material. The conditions under which it is produced appear to be in a solution of approximately the neutrality of distilled water. If barium or calcium chlorid is added to a sodium hydroxid solution of the acetyl, and the solution is boiled, no decomposition of the barium or calcium salts occurs. If magnesium chlorid is used in place of barium or calcium, the basicity of magnesium hydroxid is insufficient to prevent the decomposition of the acetyl, and there is a spontaneous liberation of iodine accompanied with production of a blue color, which changes to green, and finally to yellow. This same reaction occurs if the sodium salt of the acetyl is dissolved in distilled water and allowed to stand without the addition of sodium hydroxid. Also if the di-sodium salt is filtered on a small Buchner funnel, washed with sodium chlorid, and allowed to stand in a moist condition, there is rapid liberation of iodine and production of bluish green colors, which fade to yellow. If small pieces of the acetyl in dry form are added to water, alcohol, or pyridin containing alkali, the solution of the solid material is accompanied by decomposition in part with a liberation of iodine and discoloration. If the acetyl is dissolved in alcohol the addition of sodium hydroxid to the solution will form the sodium salt of the acetyl without decomposition or liberation of iodine. Furthermore, an alkaline solution can be added to acid with precipitation of the acetyl without decomposition. In both acid and alkaline solutions the acetyl is as stable as thyroxin, but at the neutral point a spontaneous decomposition occurs. One of the factors which affects this reaction is the mass of material present. In dilute solutions the decomposition of the acetyl is very much slower, and in sufficiently dilute solutions it may not occur at all. This effect of the mass of material explains why solution in alcohol prevents the destruction of the acetyl with addition of alkali. The mechanism is essentially the diminution of the concentration of the acetyl. Great difficulty was encountered in the preparation of the acetyl until the factors influencing the decomposition were discovered. As thyroxin does not react in this way no difficulty was anticipated, and it was only after identification of free iodine in the solutions of the acetyl which had turned bluish green that an insight into the mechanism was obtained. Why the acetyl derivative spon-

taneously decomposes at the neutral point and gives off iodine in the free form instead of hypo-iodous acid, as occurs with thyroxine, is not known.

The reactions resulting in the oxidation of the acetyl and liberation of iodine are also given by the ureid under similar conditions. This excludes the possibility that the acetyl radical is necessary for the decomposition and suggests that the reason for the instability is the replacing of the imino hydrogen by a larger group.

When this decomposition has occurred in part, the products cannot be removed from the rest of the material, and it is impossible to separate the acetyl in free form. The tarry products resulting from the decomposition of a small part prevent the crystallization of the rest of the acetyl. The retention of impurities by the acetyl is very similar to the retaining of impurities by partially purified thyroxine.

Beside the spontaneous decomposition other reactions which are specific to the acetyl were found which will be discussed at this time. It was found that when the acetyl is freshly precipitated from an alkaline solution by an acid it is soluble in ether. After it has been separated in crystalline form and dried it is insoluble in ether. This difference in solubility is undoubtedly due to the acetyl existing in open-ring form when precipitated from cold water solution. The closed-ring form is insoluble in ether.

When the acetyl derivative is prepared by adding acetic anhydride to an alkaline alcoholic solution of thyroxine and the alcoholic solution of the acetyl is then added to ether, the acetyl is removed only partially by subsequent extraction of the ether with sodium hydroxide. A large amount of the acetyl remains in the ether. If the ether solution is tested with nitrous acid the usual reaction, with the production of a yellow color turning to red with the addition of ammonia, does not occur. After alcoholic sodium hydroxide is added and the solution is heated, a typical reaction with nitrous acid will take place. Another difference of the acetyl before and after the treatment of the ether solution with alkali is shown in the solubility of the acetyl in alkalis. If the ether is evaporated before alkaline hydrolysis, the acetyl is found to be very difficultly soluble in aqueous sodium hydroxide. After hydrolysis in alkaline alcohol the acetyl is very easily soluble in dilute alkali. The non-reactivity with nitrous acid and insolubility in alkali may be due either to the formation of an inner salt between the car-



boxyl and imino, or to the formation of a di-acetyl derivative. Treatment with alkalis hydrolyzes either the acid salt or one acetyl group, and the acetyl in free form is liberated.

#### THE ACTION OF SUNLIGHT ON THYROXIN, AND THE PRODUCTION OF COLORED COMPOUNDS FROM THYROXIN

When thyroxin, the acetyl, or the ureid is dissolved in dilute sodium hydroxid and allowed to stand in the sunlight, the solution slowly changes, and in the course of from twelve to seventy-two hours develops a distinctly pink color. On further standing the pink color is changed to yellow. When the carbonic acid derivative was prepared by treating thyroxin with phosgene, it was found to be unstable and changed to a deep pink. When the sodium or barium salt of thyroxin is allowed to stand exposed to sunlight in a dry form, it also develops a pink color. With the barium salt this action does not occur in the dark, or when the salt is covered with water. The development of the pink color in each case is accompanied by the splitting off of iodine in the form of hypo-iodous acid. This pink color was first noticed on the edges and outside of white porcelain casseroles which were used to extract the barium salt of thyroxin with sodium hydroxid. Where the solution dried and was exposed to heat and light the pink color developed. Later this was shown to be due to the thyroxin itself and not to the impurities present. The chemical structure of the pink-colored compound is still unknown, but it appears probable that it is an oxidation product of the hydro-indol nucleus. The effect of light on the separation of thyroxin is of importance, and loss of thyroxin due to the action of light may amount to a considerable percentage of the total unless precautions are observed not to permit the action of direct sunlight to destroy the partially purified thyroxin.

#### EFFECT OF ACID AND ALKALI ON THYROXIN

No quantitative determinations have been made as yet concerning the ultimate products of alkaline hydrolysis because of the amount required to isolate the decomposition products. Thyroxin is not affected at room temperature by any concentration of aqueous sodium hydroxid. It is soluble in dilute alkali and after the concentration has reached from 10 to 15 per cent the di-sodium salt separates. The further addition of alkali renders the sodium salt more insoluble but it does not cause any destruction of thyroxin. Although thyroxin is

stable in sodium hydroxid at room temperature, when it is heated above  $110^{\circ}$  in the presence of strong sodium hydroxid, there is a destruction of the molecule with the splitting off of sodium iodid, and eventually the liberation of indol which may be identified by the pine-splinter reaction. The amount of indol liberated is not quantitative and it is probable that only traces of the hydro-indol nucleus appear as indol.

In acids thyroxin is not so stable as in the presence of alkali. In aqueous solutions of pure thyroxin, hydrochloric or sulfuric acids precipitate the hydrochlorid or sulfate of thyroxin, and, since these are insoluble, the destruction of thyroxin is prevented. However, when thyroxin is present in open-ring form, strong acids bring about reactions with the impurities, and oily tarry products result. In alcohol solutions prolonged action of hydrochloric acid causes a destruction in part even with pure thyroxin, resulting in the production of a brown discoloration. Polymerization of indol compounds in the presence of acid is well established, and it seems probable that this explains the destructive action of acids on thyroxin.

#### A CONSIDERATION OF OTHER POSSIBLE STRUCTURAL FORMULAS

Accepting the empirical formula as  $C_{11}H_{10}O_3NI_3$ , the carbonyl group in the molecule could be present as a ketone, either attached to the side chain or to the benzene ring. That this is not the case is shown by the failure of thyroxin to react with hydrazin, phenylhydrazin, or semicarbazone. The carbonyl group adjacent to the imino should not react with hydrazin and the failure of thyroxin to react is evidence corroborating the hypothesis that the carbonyl group is adjacent to the imino. The positions of the three iodine atoms, the three extra hydrogen atoms, and the three carbon atoms in excess of the indol nucleus have not been determined by substitution or by decomposition products. The most conclusive proof of the position of the three carbon atoms and the terminal carboxyl would be furnished by the synthesis of thyroxin. The synthesis of thyroxin will be reported in another paper, but at this time the synthesis of the compound will be cited as evidence for the correctness of the structural formula assigned in regard to the position of the three carbon atoms with terminal carboxyl. The establishment of the fact that thyroxin does not rotate polarized light excludes an asymmetric carbon atom and confirms the arrangement of the double bonds.

## THE CRYSTAL FORM AND MELTING POINT OF THYROXIN

The keto form of thyroxin crystallizes in six distinctly different forms (Figs. 223 to 228). Each of the seven other forms of thyroxin has characteristic crystal forms. The di-basic and mono-basic metal salts and the amino- and imino-acid salts of thyroxin also have characteristic forms.



FIG. 223.

FIGS. 223 to 228.—Six different types of crystals in which the keto form of thyroxin separates.

The crystal forms of imino-acid salts and of di-metal and mono-metal salts are flat plates for the most part. The other crystal forms are long branching needle blades or thread-like needles which occur in rosettes or sheaves, or in tangled masses.

Beside the type of crystal, all these forms and derivatives of thyroxin also have characteristic melting points. For these reasons microscopic study of the crystals and the determination of the melting point are the two methods which have proved of greatest value during this investigation. The determination of iodine is not of such

value because the iodine content of any one form may vary within wide limits without greatly affecting either the melting point or the crystal form. A good illustration of this is in the keto form of thyroxine. The keto form of thyroxine when pure melts at  $250^{\circ}$ , when slightly impure the melting point drops to  $246^{\circ}$  or  $245^{\circ}$ , and when grossly contaminated with impurities it drops to  $240^{\circ}$ . This point, however, appears to be the limiting value below which the keto form seldom



FIG. 224.

melts. It appears that merely dissolving thyroxine in alkali and precipitating it causes a slight decomposition. The decomposition products are retained by the pure thyroxine and are separated with great difficulty. However, the presence of these impurities rarely exceeds the amount which lowers the melting point to the neighborhood of  $240^{\circ}$ . Microscopically the keto type of crystals could be identified, and the melting point of  $240^{\circ}$  or above would confirm the form in which thyroxine existed but the iodine content might vary as much as 2.5 per cent from the theoretical. The melting point of the keto

form, from  $240^{\circ}$  to  $250^{\circ}$ , is the highest of all forms or derivatives of thyroxin. The amino carboxyl form melts in the neighborhood of  $225^{\circ}$ ; the amino hydrate melts at  $216^{\circ}$ , and the enol form at  $204^{\circ}$ ; the imino-acid salts melt at about  $228^{\circ}$ ; the amino-acid salts in the neighborhood of  $204^{\circ}$ ; the derivatives of thyroxin attached to the imino, in closed-ring form, melt at about  $238^{\circ}$  and in open-ring form at about  $152^{\circ}$ . It is apparent that the melting points of different forms



FIG. 225.

and derivatives are so widely separated that no misinterpretation could result except in cases of mixtures, and the crystal form is so definite that mixtures can be identified under the microscope. It has been found, however, that the melting point varies greatly with the rate of heating. One sample of thyroxin which melted at  $240^{\circ}$  when heated at the rate of  $10^{\circ}$  increase per minute, melted at  $248^{\circ}$  when heated at the rate of  $18^{\circ}$  increase per minute, and at  $221^{\circ}$  when heated at the rate of  $0.6^{\circ}$  increase per minute.

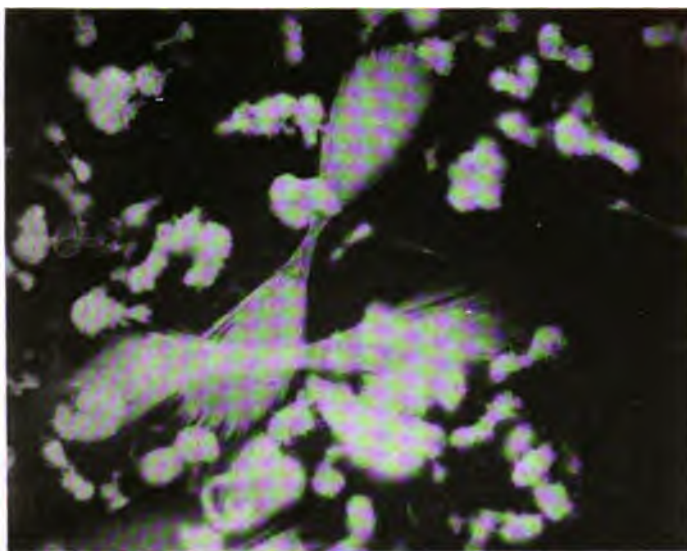


FIG. 226.



FIG. 227.

For a routine determination we have adopted the rate of  $10^{\circ}$  increase per minute, and when the melting point is observed under these conditions each form of thyroxin and its derivatives agree very closely in their melting points, with other samples of the same form.

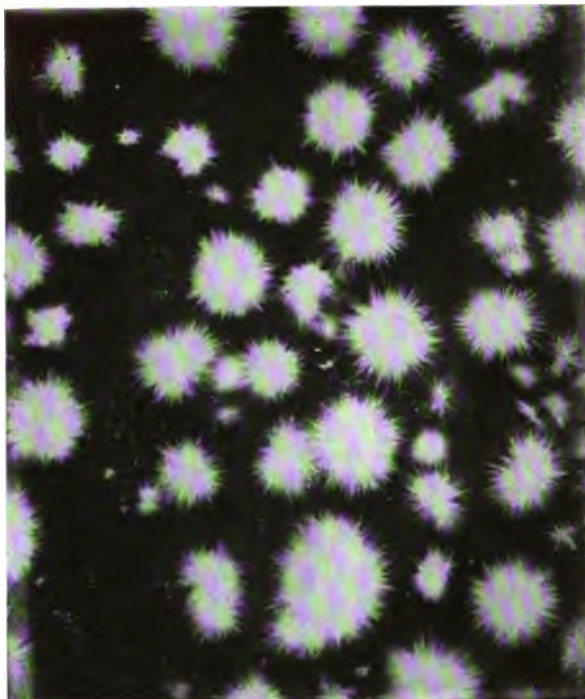


FIG. 228.

#### EXPERIMENTAL

##### *The percentage of iodine in thyroxin*

Eighteen different samples of thyroxin have been prepared, the weights of the samples ranging from 900 mg. to 5 gm. All the samples contained at least 63.5 per cent of iodine and six were purified until they contained approximately 65 per cent of iodine. The iodine content of Samples 1 to 6 is as follows:

IODIN CONTENT OF THYROXIN<sup>2</sup>

Sample 1.	5.10 mg. contained	3.31 mg. of iodine =	64.81 per cent.
" 2.	5.12 "	3.32 "	64.86 "
" 3.	5.24 "	3.41 "	65.02 "
" 4.	5.10 "	3.32 "	65.00 "
" 5.	25.3 "	16.45 "	65.00 "
" 6.	4.51 "	2.66 "	65.02 "

Solubility = one part in 48,800.

Precipitation of thyroxin from alkaline alcohol with acetic acid, or by boiling an ammoniacal solution, does not vary the percentage of iodine. Precipitated with acetic acid from alkaline alcohol the iodine content of thyroxin was 64.95 per cent. Precipitation of the same preparation by boiling an ammoniacal solution gave an iodine content of 64.92 per cent. Fifty milligrams of thyroxin were dissolved in 200 c.c. of water containing 3 c.c. of concentrated ammonium hydroxid. The solution was boiled down to 100 c.c. One hundred cubic centimeters of water were added and the solution was boiled for a few minutes, cooled, and filtered. Fifteen cubic centimeters of filtrate contained 0.20 mg. of iodine.

## ULTIMATE ANALYSIS OF THYROXIN

Sample No.	Weight of sample, mg.	Carbon dioxid, mg.	Water, mg.	Carbon per cent	Hydrogen per cent	Iodine per cent
7	201.4	175.2	32.3	23.72	1.78	64.95
7	171.2	148.0	26.9	23.57	1.74	64.95
8	291.0	248.8	45.7	23.32	1.74	64.92
9	124.2	101.9	18.5	22.37	1.65	65.02

102 mg. of thyroxin contained 2.27 mg. nitrogen = 2.23 per cent.

	Carbon per cent	Hydrogen per cent	Oxygen per cent	Nitrogen per cent	Iodine per cent
Calculated for $C_{11}H_{10}O_3NI_2$ .....	22.56	1.70	8.20	2.39	65.10
Found.....	22.37	1.65	8.73	2.23	65.02

<sup>2</sup>The iodine was determined by a method published in 1914, which has been modified recently so that it is now applicable for the determination of small amounts of iodine to a high degree of accuracy (Kendall, E. C.: The determination of iodine in connection with studies in thyroid activity, Jour. Biol. Chem., 1914, xix, 251).



## SOLUBILITY OF KETO FORM OF THYROXIN

Fifty milligrams of thyroxin were dissolved in 200 c.c. of dilute sodium hydroxid. Twenty cubic centimeters of 50 per cent hydrochloric acid were added and the solution was boiled; 15 c.c. of the filtrate contained 0.116 mg. of iodine.

Solubility = one part in 84,000.

*The sulfate of thyroxin.*—For the preparation of the sulfate 50 mg. of thyroxin are dissolved in 200 c.c. of water containing 50 to 100 mg. of sodium hydroxid; 20 c.c. of 50 per cent sulfuric acid are added, and the solution is boiled. The sulfate of thyroxin is soluble at 100°, but on cooling settles to the bottom of the container in oval-shaped plates. It may be filtered on a Buchner funnel, washed with water, and dried in a desiccator.

## ANALYSIS OF THE SULFATE OF THYROXIN

Sample 1. 5.48 mg. contained 3.27 mg. of iodine = 59.71 per cent.

" 2. 25.00 " " 15.00 " " " = 60.00 "

114.4 mg. of thyroxin sulfate gave 86.9 mg. of carbon dioxide, 18.1 mg. of water; 5.08 mg. contained 3.04 mg. of iodine.

	Carbon per cent	Hydrogen per cent	Iodine per cent
Calculated for $C_{11}H_{11}O_4NI_3S_4$ .....	20.82	1.73	60.09
Found.....	20.71	1.75	59.92

Fifty milligrams of thyroxin were dissolved in 200 c.c. of sodium hydroxid precipitated with 20 c.c. of 50 per cent sulfuric acid, and the solution was boiled; 15 c.c. of the cooled filtrate contained 0.127 mg. of iodine.

Solubility = one part in 76,900.

*The hydrochlorid of thyroxin.*—The hydrochloride of thyroxin is best prepared by dissolving a small amount of thyroxin, 15 to 25 mg., in 5 or 6 c.c. of alcohol containing 2 to 3 c.c. of 50 per cent hydrochloric acid. One to two cubic centimeters of water are added, and the alcohol is boiled off in a test-tube. After most of the alcohol has been distilled the hydrochlorid will separate in flat, glistening plates. If too small an amount of acid is used, or too much water, the hydrochlorid will hydrolyze, and the plates will change to needles.

*The metal salts of thyroxin.*—Dry crystalline thyroxin is readily soluble in sodium and potassium hydroxids in the cold, if the concentration of the alkali is less than 10 to 15 per cent. Thyroxin is in-

soluble in sodium or potassium hydroxid in the cold if the alkali is stronger than 15 to 20 per cent, but it is more soluble in strong alkali if the solution is warmed. In a mixture of 66 per cent of alcohol and 33 per cent of water containing 1 per cent of sodium hydroxid, thyroxin may be dissolved to the extent of about 4 per cent. It is still more soluble in hot solutions, but on cooling will separate as the di-metal salt. Thyroxin is not readily soluble in dilute ammonia, but concentrated ammonia will dissolve about 1.8 per cent of thyroxin.

*The di-basic sodium and potassium salts.*—One hundred milligrams of thyroxin are dissolved in 20 c.c. of dilute sodium hydroxid and to this are added 150 c.c. of a solution of 10 per cent sodium hydroxid containing 20 per cent of sodium chlorid. If a precipitate occurs the solution is warmed and the clear solution is then allowed to stand until cold. The exact concentrations of sodium chlorid and hydroxid are not important. The di-sodium salt readily separates in any solution containing a high concentration of sodium salts. If the strongly alkaline solution is decanted and replaced with 15 per cent sodium chlorid solution, the crystals may be filtered through a Buchner funnel on paper. They are insoluble in 10 to 15 per cent sodium chlorid and may be washed and dried. The di-sodium salt cannot be prepared in pure form for analysis as washing with water dissolves the salt, and it passes through the paper. The di-basic potassium salt is prepared in a manner similar to that used for the sodium salt. The di-ammonium salt is prepared by dissolving thyroxin in hot concentrated ammonium hydroxid and allowing the solution to cool. Flat, rectangular crystals of the di-ammonium salt will separate.

*The alkaline earth salts of thyroxin.*—The barium, calcium, and magnesium salts of thyroxin are prepared by dissolving 50 to 100 mg. of thyroxin in 100 c.c. of dilute sodium hydroxid, using as small an amount of alkali as possible to carry the thyroxin into solution. The solution is heated to boiling and 20 c.c. of a 20 per cent solution of barium, calcium, or magnesium chlorid are added to the hot solution of thyroxin. Carbon dioxid is excluded by placing the beaker in an atmosphere free of carbon dioxid. The magnesium and calcium salts are very slightly soluble in boiling water. Five hundred cubic centimeters of boiling water will dissolve between 100 and 150 mg. of the barium salt. The barium salt may be suspended in boiling water and the solution filtered through a Buchner funnel into a suction flask. Thirty cubic centimeters of 20 per cent barium chlorid are

now added to the filtrate and the barium salt allowed to recrystallize. Only a negligible amount of thyroxin is soluble in the presence of this amount of barium chlorid. The barium salt under these conditions is unstable and will slowly turn a pink color. Analysis for iodine shows a lower iodine content than that calculated.

#### IODINE CONTENT OF BARIUM SALT

Sample 1. 6.72 mg. contained 3.26 mg. of iodine = 48.51 per cent.

" 2. 5.98 " " 3.00 " " " = 50.24 "

Calculated for  $\text{BaC}_{11}\text{H}_9\text{O}_3\text{NI}_3$ : 52.91 per cent.

If the barium salt is filtered and dried there is a slow decomposition and the color of the salt becomes yellowish gray.

*Silver, copper, nickel, and zinc salts of thyroxin.*—The silver, copper, nickel, and zinc salts are prepared by dissolving 50 to 100 mg. of thyroxin in 25 to 50 c.c. of concentrated ammonia. Twenty-five cubic centimeters of a 10 per cent solution of silver nitrate, copper sulfate, nickel sulfate, or zinc sulfate are made ammoniacal with strong ammonia so that the precipitated hydroxide is just carried into solution, and there is a slight excess of ammonia. The solution of the metal is now added to the ammoniacal solution of thyroxin, and after standing a short time the crystals of the metal salt will separate. If too much ammonia is used, a larger amount of the solution of the metal may be required to start the crystallization. Allowing it to stand over night will insure a more complete precipitation. Sodium hydroxide may be used for the solution of thyroxin, but, since the metal salt of thyroxin is more soluble in sodium hydroxide, ammonium hydroxide has been found to be the most satisfactory solution. The silver, copper, nickel, or zinc salts suspended in water or dilute ammonia are soluble on the addition of several cubic centimeters of 30 per cent sodium hydroxide solution.

#### IODINE CONTENT OF SILVER SALT

Sample 1. 4.86 mg. contained 2.37 mg. of iodine = 48.74 per cent.

" 2. 4.96 " " 2.44 " " " = 49.15 "

" 3. 4.00 " " 1.97 " " " = 49.34 "

" 4. 4.06 " " 1.99 " " " = 49.10 "

" 5. 4.54 " " 2.23 " " " = 49.20 "

" 6. 4.08 " " 1.96 " " " = 48.00 "

" 7. 6.02 " " 2.93 " " " = 48.60 "

" 8. 4.38 " " 2.09 " " " = 47.73 "

Calculated for  $\text{Ag}_2\text{C}_{11}\text{H}_9\text{O}_3\text{NI}_3$ : 47.74 "

" "  $\text{AgC}_{11}\text{H}_9\text{O}_3\text{NI}_3$ : 55.06 "

The average of these eight determinations is 48.73 per cent iodine. The iodine content indicates the addition of 92 per cent of the theoretical amount for a di-metal salt and 184 per cent of the amount required for a mono-metal salt. The higher iodine content than that calculated for a di-metal salt is undoubtedly due to the hydrolysis of the hydroxy group. In the zinc salt, the amount of iodine was found to be 56.95 per cent. The calculated amount for the zinc salt is 58.79 per cent, but the calculated amount of iodine in the zinc salt in which hydrolysis of the hydroxy group had occurred would be 57.12 per cent. The close agreement between the amount found and the latter figure is evidence that hydrolysis of the hydroxy group also occurs in the zinc salt of thyroxine. The low iodine content of the salts of the diad metals, barium and zinc, and the high iodine content of the salt of the monad metal, silver, suggest that in all di-metal salts of thyroxine hydrolysis of the hydroxy group is brought about by washing the salt with water.

*Preparation of monometal salts.*—One hundred milligrams of thyroxine are dissolved in 150 c.c. of 1 per cent sodium hydroxide, and carbon dioxide is bubbled through the solution until thyroxine is precipitated. The suspension is now heated until solution is complete. On cooling, the mono-sodium salt separates in crystal form. The separation of the mono-salt is assisted by the presence of sodium salts and is hindered by too great a dilution. An excess of carbon dioxide must not be passed through the solution, as free thyroxine will be precipitated. The preparation of the potassium salt is similar to that of the sodium salt. In preparing the ammonium salt, strong ammonium hydroxide is much better than dilute, as the solubility of the ammonium salt is thereby decreased. If the mono-metal salt is filtered on a Buchner funnel and washed with 10 to 15 per cent sodium, ammonium, or potassium chloride, it is not dissolved through the paper. If washed with cold water, about 40 per cent is dissolved and 60 per cent of the amount of thyroxine taken remains on the paper in the form of free thyroxine in the enol form.

#### NESSLERIZATION OF THE HYDROLYZED MONO-AMMONIUM SALT OF THYROXIN

Fifty milligrams of the residue left on the paper after washing the mono-ammonium salt with water were dissolved in 60 c.c. of ammonia-free water containing a small amount of sodium hydroxide. The

addition of 15 c.c. of Nessler's solution and dilution to 100 c.c. produced no color, showing that hydrolysis of the mono-ammonium salt was complete.

*Solubility of mono-sodium salt.*—Five cubic centimeters of 0.10 per cent sodium carbonate dissolved about 15 mg. of dry thyroxin in keto form, when the solution was heated to boiling. Most of the thyroxin reprecipitated on cooling to 20°, but not as the mono-sodium salt. The crystals were needles or very small rosettes. One cubic centimeter of the filtrate contained 0.76 mg. of iodine = 1.17 mg. of thyroxin.

Solubility = one part in 850.

Five cubic centimeters of 1 per cent sodium carbonate dissolved 85 to 90 mg. of thyroxin at almost the boiling point. Probably more than this amount could be dissolved but as the solution began to turn yellow the heating was stopped. On cooling to 23°, needles in clusters and square plates of mono-sodium salt separated. One cubic centimeter of filtrate contained 1.14 mg. of iodine = 1.75 mg. of thyroxin.

Solubility = one part in 570.

*The enol form of thyroxin.*—The enol form of thyroxin is the most difficult to prepare in crystalline form, but is very easily prepared in the crystal form of the mono-metal salts by cold water hydrolysis of the mono-ammonium sodium, or potassium salts. Ten to twenty milligrams of the enol form in dry powder is readily soluble in 1 to 2 c.c. of pyridin. The addition of 10 to 15 c.c. of water will produce a cloudiness. On long standing (twenty-four hours), the thyroxin will precipitate. Depending on conditions of the concentration of pyridin and the amount of thyroxin present, the thyroxin may precipitate in keto form. This may be distinguished under the microscope as long bundles, or sheaves of needles. The enol form separates in either rosettes or short bundles of needles. The enol form of thyroxin is also soluble in quinolin. Other ways to prepare the enol form of thyroxin is to add ammonium chlorid to a cold solution of the di-sodium salt in water which does not contain an excess of alkali, or to dissolve the di-sodium salt of thyroxin in alcohol and add water and ammonium chlorid. A mixture of both keto and enol crystals usually results if much alcohol is present.

Ten to fifteen milligrams of dry crystals of the keto form of thyroxin may be boiled with 5 to 10 c.c. of pyridin without going into solution. The addition of a very small amount of dilute ammonia will change the thyroxin to the enol form and carry it into solution. The water

may then be boiled off and the enol form remains soluble in pyridin. If 15 to 20 mg. of the enol form of thyroxin are dissolved in 2 to 3 cc. of pyridin in a test-tube, and to this 10 to 15 c.c. of water are added, and the solution is boiled, after the pyridin has been removed by distillation, thyroxin will separate in the keto form similar to the precipitation of thyroxin from a boiling ammoniacal solution.

Twenty-five milligrams of thyroxin added in the keto form to 10 c.c. of water in the presence of 1 gm. of sodium carbonate will not dissolve. If alcohol is used instead of water and the alcohol is boiled, the sodium carbonate does not dissolve but the thyroxin is carried into solution. The mono-sodium salt of thyroxin in the enol form produced by the alcoholic suspension of sodium carbonate is readily soluble in alcohol.

*The amino-acid salt form of thyroxin.*—For the preparation of amino-acid salts, thyroxin is dissolved in a small amount of sodium hydroxid in a large volume of water, and to this carbon dioxid or other organic acid is added until thyroxin precipitates. The voluminous precipitate is filtered, washed, and dried. In order to prepare the amino salts in crystalline form, other expedients may be used. For the preparation of the amino sulfate, thyroxin is dissolved either in formic acid or in alcohol containing a small amount of sulfuric acid. The alcohol is concentrated to small volume, and water is quickly added in large volume.

#### SOLUBILITY OF THYROXIN IN AMINO-SALT FORM

*Hydrochlorid.*—Fifty milligrams of thyroxin were dissolved in 200 c.c. of dilute sodium hydroxid, and precipitated at 25°C. with a slight excess of hydrochloric acid; 15 c.c. of the filtrate, after removing the precipitate of thyroxin, containing 0.037 mg. of iodine.

Solubility = one part in 263,000.

*Carbonate.*—Fifty milligrams of thyroxin were dissolved in 200 c.c. of dilute sodium hydroxid, and precipitated by passing carbon dioxid through the solution; 15 c.c. of the filtrate contained 0.012 mg. of iodine.

Solubility = one part in 815,000.

#### IODINE CONTENT OF AMINO CARBONATE

5.8 mg. contained 3.137 mg. of iodine = 50.57 per cent.

Calculated for  $C_{11}H_{12}O_4NI_2(H_2CO_3)\frac{1}{2}$  = 60.09 per cent.

The slightly higher figure for iodine than the calculated amount is probably due to separation of the thyroxin in either the enol or

amino-hydrate form, or to the hydrolysis of the amino carbonate and formation of the amino carboxyl. This sample of thyroxin contained 65.02 per cent of iodine when precipitated in keto form.

*The amino carboxyl form of thyroxin.*—The amino carboxyl form is prepared by suspending the amino-acid salt form of thyroxin in water in the presence of a small amount of weak organic acid, such as acetic, and boiling the solution. The acid radical is expelled from the amino group, and the adjacent carboxyl group forms an amino carboxyl salt. It can also be prepared by dissolving the di-sodium salt of thyroxin in a large volume of water, heating to boiling, adding ammonium chlorid, and continuing the boiling. The amino carboxyl form of thyroxin separates.

If no acid is present the elements of water may be expelled from the molecule and thyroxin will separate in keto form.

#### IODINE CONTENT OF HYDROLYZED AMINO-ACID SALTS

A sample of amino carbonate was suspended in neutral distilled water and the solution was boiled three minutes. This was not sufficiently long to complete the hydrolysis.

Five and thirty-eight hundredths milligrams contained 3.321 mg. of iodine = 61.72 per cent. The same sample boiled fifteen minutes showed that all the carbonate had been expelled and also that some of the amino carboxyl form had been converted into the keto form.

Five and two-tenths milligrams contained 3.305 mg. of iodine = 63.56 per cent. A sample of amino sulfate suspended in distilled water and boiled more nearly approximated the amino carboxyl form, but in this case all the sulfate radical was not hydrolyzed.

5.0 mg. contained 3.135 mg. of iodine = 62.72 per cent.				
Calculated for amino carbonate:	60.09	"	"	iodine.
" " " sulfate:	58.43	"	"	"
" " " carboxyl:	63.18	"	"	"

*Preparation of the amino hydrate form.*—Thyroxin is dissolved in a large volume of water with a moderate excess of sodium hydroxid. The solution is heated to boiling and then removed from the flame, and 10 per cent ammonium chlorid is slowly added to the amount of 10 to 15 c.c. The solution becomes turbid, and long branching crystals separate. The limits of the concentration of the hydrogen ion and the temperature for the formation of the enol, amino hydrate,

amino carboxyl, and the keto forms are very narrow. If thyroxin is dissolved in a few milligrams of sodium hydroxid, and the solution is diluted to about 400 c.c., and divided into four equal parts, each of the four different forms of thyroxin may be prepared from these solutions merely by varying the conditions of the precipitation. Ammonium chlorid added to one of the solutions in the cold will precipitate the thyroxin in the enol form, or as the mono-ammonium salt in flat plates. If ammonium chlorid is added to the second solution, which has been heated to boiling, and then removed from the flame the amino hydrate form will separate. If the amino hydrate is precipitated in the third, and the solution containing a suspension of the amino hydrate is heated to boiling and the boiling continued, the crystals will change into the amino carboxyl form. If a large excess of ammonium chlorid is added to the fourth solution, and the solution is boiled, thyroxin will separate in the keto form.

*Open-ring form in the presence of impurities.*—The percentage of iodine in the open-ring form of thyroxin, which is still soluble in pyridin, sodium carbonate, barium hydroxid and alcohol, may be between 50 and 60 per cent.

#### IODINE CONTENT OF THYROXIN STILL IN OPEN-RING FORM

Sample 1.	5.00 mg.	contained 2.51 mg. of iodine	= 50.28 per cent
" 2.	3.92 "	" 2.13 " " "	= 54.21 " "
" 3.	6.44 "	" 3.51 " " "	= 54.46 " "
" 4.	4.16 "	" 2.43 " " "	= 58.53 " "

The solubility of these samples in alcohol, sodium carbonate, and barium hydroxid showed that although the amount of impurities present was very small, the ring still existed in open form.

*Colloidal substances producing the open-ring form of thyroxin.*—Fifty to 100 mg. of pure thyroxin, added to the impurities which are separated during the process of purification, will become readily soluble in alcohol, sodium carbonate, and barium hydroxid, showing the change from the keto to the open-ring form. Gelatin and proteins of blood produce the same changes, but the amino-acids resulting from the hydrolysis of gelatin will not change the solubility of thyroxin in barium hydroxide, alcohol, or sodium carbonate.

#### THE ACETYL DERIVATIVE

*Preparation of the acetyl.*—In the preparation of the acetyl it is necessary to use pure thyroxin. The presence of even a small amount of impurities makes it impossible to crystallize the acetyl



and it will separate only as an oily tar. One hundred milligrams of pure thyroxin are added to 20 c.c. of alcohol containing 100 mg. of sodium hydroxid. After the thyroxin is entirely dissolved 2 c.c. of acetic anhydrid are added. The solution is allowed to stand thirty minutes, 5 c.c. of water and 5 c.c. of 50 per cent sulfuric acid are added, and the alcohol is evaporated by boiling in a 200 c.c. distilling flask under diminished pressure. The temperature is not allowed to go above 40°C. Crystals of the sulfate of the acetyl separate as the alcohol is removed. These are dissolved in about 15 c.c. of alcohol which is filtered and added to a beaker containing 200 c.c. of boiling water and 5 c.c. of 50 per cent sulfuric acid. The addition of the first few drops of the alcohol solution of the acetyl does not cause a precipitate, but further addition of the alcohol solution causes a precipitation in crystalline form of the free acetyl.

Purification of the acetyl may also be carried out by dissolving the acetyl sulfate in 25 c.c. of alcohol and adding 5 gm. of sodium acetate and 10 c.c. of 30 per cent sodium hydroxid. After the alcohol has been removed by boiling under diminished pressure, the di-sodium salt of the acetyl will separate in large, flat plates. The sodium salt may then be dissolved in alcohol and precipitated by addition to a boiling solution of dilute sulfuric acid as described above.

Many samples of the acetyl have been prepared and analyzed. Some of the results are as follows:

## ANALYSIS OF THE ACETYL OF THYROXIN

Sample 1.	5.26 mg. contained	3.20 mg. of iodine	= 60.91 per cent.
" 2.	5.20 "	3.17 "	" " = 60.96 "
" 3.	5.12 "	1.90 "	" " = 60.85 "
" 4.	5.12 "	3.11 "	" " = 60.67 "
" 5.	5.16 "	3.14 "	" " = 60.83 "
" 6.	5.10 "	3.11 "	" " = 60.93 "
" 7.	5.10 "	3.09 "	" " = 60.61 "
" 8.	5.04 "	3.05 "	" " = 60.52 "
" 9.	5.02 "	3.05 "	" " = 60.74 "

97.9 mg. of acetyl gave 90.1 mg. of carbon dioxide and 16.2 mg. of water; 5.10 mg. contained 3.10 mg. of iodine.

	Carbon per cent	Hydrogen per cent	Iodine per cent
Calculated for $C_{13}H_{12}O_4NI_3$ .....	24.88	1.93	60.77
Found.....	25.09	1.85	60.86

*The sulfate of the acetyl derivative.*—If the acetyl derivative is dissolved in alcohol and added to boiling dilute sulfuric acid, the acetyl precipitates in free form without the addition of sulfuric acid attached to the imino group. If, however, sulfuric acid is added to the alcohol solution of the acetyl and the alcohol is evaporated at either room temperature, by a current of air or by boiling under diminished pressure at a low temperature, the sulfate of the acetyl separates in needle crystals.

## ANALYSIS OF THE SULFATE OF THE ACETYL

Sample 1.	5.02 mg.	contained 2.84 mg. of iodine	= 56.66 per cent.
" 2.	5.52 "	" 3.12 " " "	= 56.52 " "
" 3.	6.2 "	" 3.51 " " "	= 56.61 " "

111.5 mg. of the sulfate of the acetyl gave 94.8 mg. of carbon dioxide and 19.7 mg of water; 5.52 mg. contained 3.12 mg. of iodine.

	Carbon per cent	Hydrogen per cent	Iodine per cent
Calculated for $C_{13}H_{13}O_6NI_2S_4$ .....	23.07	1.92	56.36
Found.....	23.18	1.91	56.52

Although thyroxine is insoluble in pyridine, alcohol, ethyl acetate, or acetic acid, the acetyl is soluble in all of these reagents. When the acetyl is precipitated from an alkaline solution by the addition of an acid, it is at first soluble in ether and may be extracted out of the water by placing in a separatory funnel with ether. After the acetyl has been prepared in pure form and dried, it is insoluble in ether.

*The di-metal derivatives of the acetyl.*<sup>3</sup>—The sodium, ammonium, and potassium salts of the acetyl are prepared as with thyroxine. One hundred milligrams of the acetyl are dissolved in 10 c.c. of alcohol, to which are added 10 c.c. of 30 per cent sodium hydroxide and 5 gm. of sodium acetate. The di-metal salt will separate in large, flat crystals if the alcohol is evaporated under diminished pressure. The temperature may be raised to that of boiling water without decomposition of the acetyl by the sodium hydroxide as no hydrolysis of the acetyl occurs under these conditions. If sodium chloride is substituted for

<sup>3</sup> In working with the acetyl, it is always necessary to dissolve the dry powder in alcohol before making it alkaline. Unless this is done, some of the acetyl will spontaneously decompose during the solution of the powder in alkali.

sodium acetate in a solution similar to the one mentioned above and the alcohol is evaporated, the sodium salt of thyroxin separates in small plates.

The barium and calcium salts of the acetyl are prepared by dissolving 25 to 50 mg. of the acetyl in the least possible amount of alcohol, 2 to 3 c.c., adding water and 0.5 to 1 c.c. of pyridin; the solution is boiled until the alcohol is volatilized, care being taken not to decompose the acetyl by prolonged boiling. To the pyridin solution of the acetyl a 40 per cent solution of barium or calcium chlorid is slowly added, and the solution is heated to boiling. The alkaline earth salt of the acetyl will separate. It is readily soluble in an excess of pyridin. If the solution is heated for too long a time hydrolysis will occur. The salt may be filtered and washed without decomposition.

The reactions of thyroxin indicate that the molecule exists in both open- and closed-ring forms. The chemical properties of the acetyl are evidence that this derivative also exists in open- and closed-ring forms. The sodium salt of the acetyl washed with dilute acetic acid is completely hydrolyzed. When prepared in this way, however, its melting point is found to be 152°. When this material is dissolved in alcohol and added to boiling dilute sulfuric acid, the acetyl separates in closed-ring form, and the melting point is 238°. This suggests that in the sodium salt the acetyl exists in open-ring form, and hydrolysis of the sodium from the molecule leaves the open-ring structure. This is further corroborated by analysis of the silver salt.

*Preparation of the silver salt of the acetyl.*—If the acetyl is dissolved in alcohol and then made alkaline with sodium hydroxid and the alcohol evaporated, the addition of ammonia and silver nitrate produces no precipitate. This is also true of thyroxin in the open-ring form. If 50 mg. of the acetyl are dissolved in 2 to 3 c.c. of alcohol, to which are added 2 to 3 c.c. of pyridin and 10 c.c. of water, and the alcohol is removed by boiling, the addition of silver nitrate to the aqueous pyridin solution of thyroxin will cause a precipitate to form. This is not crystalline in nature, although under some conditions it may be possible to separate it in crystal form. The silver salt may be filtered on a Buchner funnel and washed with water without decomposition.

5.14 mg. of the silver salt of the acetyl contained 2.26 mg. of iodine = 44.06 per cent.

Calculated for  $\text{Ag}_2\text{C}_{12}\text{H}_{12}\text{O}_6\text{NI}$ , iodine = 44.35 per cent.

“ “  $\text{AgC}_{12}\text{H}_{11}\text{O}_4\text{NI}_2$  = 51.91 “ “

The iodine content of the silver salt of the acetyl indicates the addition of 2 per cent too much silver for the di-silver salt of the open ring form of the acetyl, and 220 per cent too much silver for the mono-salt of the closed-ring form. These results, proving conclusively that not one but two atoms of silver had added to the acetyl, show that in an alkaline solution the acetyl exists in open-ring form.

The open-ring structure of the acetyl is also indicated by the increased solubility of the acetyl in weak bases such as pyridin, quinolin, and very dilute ammonia. The terminal carboxyl in thyroxin is so weak that the acetyl derivative would not be soluble in these reagents in the closed-ring form.

*Preparation of the ureid.*—Only pure thyroxin should be used in preparation of the ureid for the same reasons given under the preparation of the acetyl. One hundred milligrams of di-sodium or zinc salt of thyroxin are added to 10 to 15 c.c. of glacial acetic acid containing 200 mg. of potassium cyanate. Solution of the salt of thyroxin should be completed as the ureid is soluble in acetic acid. Five cubic centimeters of water, 5 c.c. of alcohol, and 5 c.c. of 50 per cent sulfuric acid are added and the alcohol, water, and acetic acid are removed under diminished pressure, the same as in the preparation of the acetyl. The sulfate of the ureid is dissolved in 15 c.c. of alcohol, filtered, and slowly added to a beaker containing 200 c.c. of water and 5 c.c. of 50 per cent sulfuric acid, which is heated to boiling. The ureid separates in crystal rosettes or needles.

Sample 1.	4.78	mg. of ureid	contained	2.91	mg. of iodine	=	69.81	per cent.
"	2.	5.04	" " "	"	3.07	" " "	=	61.03 " "
"	3.	5.02	" " "	"	3.05	" " "	=	60.74 " "

Calculated for  $C_{12}H_{11}O_2N_2I_2$  = 60.67 per cent.

*Preparation of the methyl ester.*—One hundred milligrams of the silver salt of thyroxin are suspended in 20 c.c. of alcohol to which are added 4 to 5 c.c. of methyl iodide. The crystals are occasionally stirred and allowed to stand at a temperature of 40° to 50° for several hours until decomposition of the silver salt is complete. This is indicated by separation of silver iodide in voluminous form. The silver iodide is removed by filtration. If the alcohol is allowed to evaporate, the dimethyl derivative crystallizes in the form of fine threads. They may be separated by formation of the sulfate similar to the preparation of the acetyl. Five cubic centimeters of water and

5 c.c. of 50 per cent sulfuric acid are added to the alcohol filtrate from the silver iodid and the alcohol is removed by distillation under diminished pressure. The dimethyl derivative separates probably as the sulfate. It is insoluble in water, but soluble in alcohol. Treatment with alcoholic sodium hydroxid frees the carboxyl group, and the monomethyl derivative is then slightly soluble in aqueous sodium hydroxid. The methyl ester is very difficultly purified and has not been prepared containing a theoretical percentage of iodine. It appears to retain silver iodid even after repeated precipitation.

*The action of nitrous acid on thyroxin.*—Twenty-five milligrams of thyroxin dissolved in 2 c.c. of dilute sodium hydroxid were added to the de-aminizing chamber of the Van Slyke apparatus, and the usual procedure was followed, shaking for three minutes; 0.69 c.c. of nitrogen was evolved. The apparatus was allowed to stand nine minutes and was again shaken for three minutes; 0.06 c.c. of nitrogen was obtained. Four minutes later it was again shaken for three minutes and 0.04 c.c. was obtained. The total, liberated in twenty-two minutes, showed 1.72 per cent amino nitrogen which is 72 per cent of the total nitrogen contained in the molecule.

Another 25 mg. sample of thyroxin, after three minutes' shaking, liberated 0.75 c.c. of nitrogen. This is equivalent to 1.60 per cent of amino nitrogen in the molecule and is 67 per cent of the total nitrogen.

Twenty-five milligrams of the amino carboxyl salt form of thyroxin suspended in 2 c.c. after three minutes shaking gave 0.08 c.c. ten minutes later; after three minutes more shaking, 0.06 c.c.; and ten minutes later, after three minutes shaking, 0.04 c.c.; total amount liberated = 0.18 c.c. which is equivalent to 0.093 mg. of amino nitrogen, and is 16 per cent of the total nitrogen. Ten milligrams of keto form of thyroxin suspended in 2 c.c. of water gave no amino nitrogen.

The amino nitrogen in 25 mg. of the acetyl was determined as described above. After three minutes 0.11 c.c., and after ten and one-half minutes, 0.11 c.c. more of nitrogen was liberated. The nitrogen in the amino form amounted to 24 per cent of the total nitrogen in the molecule.

The nitrogen in isatin and indol, given off as amino-nitrogen, was determined. One hundred milligrams of isatin after four minutes gave 1.72 c.c. and after five minutes more gave 0.41 c.c. of nitrogen. This volume was equivalent to 1.13 mg. of nitrogen and amounted to 12 per cent of the total nitrogen present. One hundred milligrams of

indol gave 1.27 c.c. after three minutes, and 0.34 c.c. of nitrogen after four minutes more shaking. This is equivalent to 0.86 mg. and is 7 per cent of the total nitrogen in indol.

Beside the action of nitrous acid on thyroxin, liberating some of the nitrogen as amino nitrogen, a characteristic color reaction is produced. A few milligrams of pure thyroxin, added to 5 c.c. of alcohol containing three to four drops of 50 per cent hydrochloric acid to which are added five to six drops of 1 per cent sodium nitrite solution, will develop a yellow color. This is increased by boiling. If the solution is cooled and concentrated ammonia is added until distinctly alkaline, a pink color is obtained. This is a sensitive reaction for thyroxin, a color being produced by one part of thyroxin in 40,000 part solution. If acetic or sulfuric acid is substituted for hydrochloric, the yellow color is not so deep and the addition of ammonia does not produce a pink color but gives a yellowish orange color. If the sample of thyroxin is impure, a yellow instead of a pink color is produced with ammonia. The acetyl and ureid derivatives give the same reaction, producing a pink color with ammonia.

*The pine-splinter reaction for indol.*—From 15 to 20 mg. of thyroxin are placed in a test-tube with 5 c.c. of 30 per cent sodium hydroxid and sufficient water to carry the thyroxin into solution. As the excess of water is boiled off, thyroxin will precipitate as a di-sodium salt, but on further heating, after the water has been almost completely driven off and the temperature of the solution has been raised to between 100° and 200°, the di-sodium salt is again dissolved and a faint indol-like odor is given off. A pine-splinter moistened with hydrochloric acid is turned red by the vapors given off from the fusion.

*The effect of thyroxin on polarized light.*—One gram of thyroxin was dissolved in 20 c.c. of alcohol and 7 c.c. of water containing 300 mg. of sodium hydroxid. The solution was filtered and placed in a 2 dm. tube and its effect on polarized light was determined. No rotation of light could be determined. The solution of thyroxin was then placed in a 1 dm. tube. Under these conditions there was no measurable rotation of light.

*The effect of hydrazine on thyroxin.*—If thyroxin is added to hydrazin hydrate, it immediately dissolves. If water is added, thyroxin remains in solution. The addition of carbon dioxid precipitates thyroxin as the amino carbonate. If the solution of thyroxin in the hydrazin hydrate is boiled after the addition of water, thyroxin

precipitates as from ammoniacal solution. No condensation with hydrazin, phenylhydrazin, semicarbazone, or hydroxylamin could be demonstrated when thyroxin was dissolved in alkaline alcohol to which these reagents were added, in acid alcohol to which these reagents were added, together with sodium carbonate or pyridin, or when dissolved in pyridin to which the reagents were added. Either decomposed products due to heating at too high temperature or unchanged thyroxin were recovered.

*The melting points of thyroxin and its derivatives.*—The following melting points of thyroxin in its several forms and its derivatives are recorded to illustrate the agreement between different samples (Tables 1 to 9). It is evident that among some of the derivatives fairly large variations occur, but between any two different forms the differences are much greater than that found between the melting points of two samples of the same derivatives.

The following salts of thyroxin and its derivatives were not melted when heated to 260°: di-sodium and mono-sodium salt of thyroxin; di-potassium and mono-potassium salt of thyroxin; barium salt of thyroxin; di-silver salt of thyroxin; di-sodium salt of acetyl; di-silver salt of acetyl; calcium salt of acetyl.

TABLE 1.—THE MELTING POINT OF THE KETO FORM OF THYROXIN

No. of sample	Slight browning	Sublime or mist	First droplets	Completely melted	Froth
125			248	250	250
32			241	248	248.9
123			235	247	247
124			240	246	246
81			243	245	246
91			241	242	243
107			241	242	242
115			239	242	242
119			239	241	241.5
117			237	241	241
97			236	240	241
28			195	240	241.5
80			239	240	240
59			238	239	240.5
51			236	239	240

TABLE 2.—THE MELTING POINT OF THE ENOL FORM OF THYROXIN

No. of sample	Slight browning	Sublime or mist	First droplets	Completely melted	Froth
40	190		200	202	205
41	180		200	205	205
42	190		200	204.5	204.5
43	160	190	200	204	204
44	160	190	202	208	208
46	170	190	200	202	204
49	165	190	203	206	206
50	165		196	201	201
53	150		198	203	204
55	160	190	200	202	204
108	160		198	204	205
109	180	198	206	208	208
110	170		200	202	203
111				203	205

TABLE 3.—THE MELTING POINT OF THE AMINO HYDRATE FORM

No. of sample	Slight browning	Sublime or mist	First droplets	Completely melted	Froth
129			214	216	216.5
114			207	212	214

TABLE 4.—THE MELTING POINT OF THE AMINO CARBOXYL SALT FORM

No. of sample	Slight browning	Sublime or mist	First droplets	Completely melted	Froth
86	215		219	220	221
88			216	218	221
89			216	218	219
95			219.5	221	222
100			222	223.5	223.5
105			222	223	223.5
112			216	220	221
113			217	221	222
118			221	222	222.5
120			221	224	224
121			222	224	225
127			218	222	223
130				225.5	226



TABLE 5.—THE MELTING POINT OF ACID SALTS OF THE AMINO GROUP

	No. of sample	Slight browning	Sublime or mist	First droplets	Completely melted	Froth
Amino sulfate.....	83		182	207	208	208.5
“ “.....	93	162		202	204	204
“ “.....	103	180		206	207	208
Amino oxalate.....	104	180		206	207	208
Amino formate.....	101			202	205	208
“ “.....	76	150		190	203	206.5
“ “.....	84		180	202	204	204
“ “.....	82	160			204	205
Amino acetate.....	102			202	205	208
Amino carbonate.....	87	160		204	206	206

TABLE 6.—THE MELTING POINT OF THE ACETYL

No. of sample	Slight browning	Sublime or mist	First droplets	Completely melted	Froth
34			220	223	230
30			225	235	236
29			215	223	232

TABLE 7.—THE MELTING POINT OF THE SULFATE OF THE ACETYL

No. of sample	Slight browning	Sublime or mist	First droplets	Completely melted	Froth
27			111	150	200
25				122	190
24			100	106	150

TABLE 8.—THE MELTING POINT OF THE ACETYL IN OPEN-RING FORM

No. of sample	Slight browning	Sublime or mist	First droplets	Completely melted	Froth
8			150	160	174
35				155	155
11			146	152	216

TABLE 9.—THE MELTING POINT OF THE UREID

No. of sample	Slight browning	Sublime or mist	First droplets	Completely melted	Froth
21				225	225

## SUMMARY

The most important physical and chemical properties of thyroxin may be summarized as follows:

1. Thyroxin is a colorless, odorless, crystalline substance, insoluble in aqueous solutions of all acids, including carbonic. It is soluble in sodium, ammonium, and potassium hydroxids, and is very slightly soluble in sodium and potassium carbonate. Besides forming salts with metals, thyroxin also forms salts with acids.

2. The iodine content of thyroxin and the iodine content of the sulfate salt were found to be 65 and 60 per cent respectively. This established the molecular weight of 585. Ultimate analysis and a study of the derivatives of thyroxin show the structural formula to be 4, 5, 6 tri-hydro-4, 5, 6 tri-iodo-2 oxy-beta-indol propionic acid.

3. In the presence of alkali metal hydroxids, thyroxin forms di-basic salts through the carboxyl and hydroxy groups. In the presence of carbonates, thyroxin forms mono-basic salts with the carboxyl group alone. The imino group forms salts with mineral and formic acids but not with acetic. The salts of mineral acids are soluble in alcohol, but no acid salt of thyroxin is appreciably soluble in water. Thyroxin forms derivatives through the amino nitrogen, such as the acetyl and ureid, and through its carboxyl and hydroxy groups, such as the di-methyl derivative.

4. Thyroxin exists in four distinct forms: (1) The keto form with the imino carbonyl groups, melting point  $250^{\circ}$ ; (2) the enol form in which the hydrogen migrates from the imino to the carbonyl forming the hydroxy group, melting point  $204^{\circ}$ ; (3) an open-ring form in which the elements of water enter the molecule between the imino and carbonyl groups forming an open-ring structure with amino and carboxyl groups, which exist in salt formation, called the amino carboxyl salt form, melting point  $225^{\circ}$ ; and (4) a tautomeric form of this in which the elements of water add to the nitrogen, making the amino hydrate form, melting point  $216^{\circ}$ . If an acid is added to an enol form of thyroxin, the ring opens and the acid forms an amino-acid salt. The reason why weak organic acids including carbonic can add to the nitrogen of thyroxin-forming amino salts is that the ring is unstable in neutral aqueous solutions and the nitrogen tends to exist in the pentad state, adding either the elements of water and forming an amino hydrate, or adding a carboxyl and forming an amino salt.

These reactions could occur only with a strongly basic group. The amino group of anilin and the imino group of indol or isatin are too feebly basic to react the same as thyroxin with weak organic acids.

5. Thyroxin is not easily oxidized or reduced, but will yield to both oxidation and reduction if sufficiently strong agents are used.

6. In alkaline solutions the iodine is broken off from the thyroxin molecule, not as free iodine, but as hypo-iodous acid. This reaction is accelerated by sunlight. Sunlight also produces pink color compounds from the colorless thyroxin molecule.

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## THE BASAL METABOLIC RATE IN EXOPHTHALMIC GOITER WITH A BRIEF DESCRIPTION OF THE TECHNIC USED AT THE MAYO CLINIC\*

IRENE SANDIFORD

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"In each mammal there is a basal metabolism."<sup>19</sup> By the term "basal metabolism" or better, "basal metabolic rate," of an organism is meant the minimal heat production of that organism, measured from twelve to eighteen hours after the ingestion of food and with the organism at complete muscular rest. This minimal heat production may be determined directly by actual measurement by means of a calorimeter, or indirectly, by calculating the heat production from an analysis of the end products which result from oxidation within the organism, or specifically, from the amount of oxygen used and the corresponding amount of carbon dioxid produced, together with the total nitrogen eliminated in the urine (although, for clinical work, the urinary nitrogen may be neglected).

The experimental work of Lavoisier<sup>17</sup> marks the beginning of researches on metabolism and to him belongs the conception that the life processes are those of oxidation with the elimination of heat. Technically, the problem was beset with many difficulties for it was necessary not only to measure the amount of heat lost by radiation and conduction from the body (direct calorimetry), but also to collect accurately the various end products resulting from combustion within the body, from which data the heat production can be calculated (indirect calorimetry), in order to prove from a comparison of the results obtained from the two methods that the law of conservation of energy also holds for the living organism. Furthermore, before the method of indirect calorimetry could be employed the heat values of carbohydrate, fat, and protein had also to be determined in order to calculate the heat derived from their combustion in the body. The solution of these problems was greatly advanced by Carl Voit<sup>23</sup> and

\* Reprinted from *Endocrinology*, 1920, iv, 71-87.

his pupils, the chief of whom were Pettenkofer<sup>22</sup> and Rubner.<sup>27</sup> The heat values of carbohydrate and fat were readily determined by Rubner<sup>25</sup> since these two substances are oxidized to the same end products (carbon dioxide and water) whether burning in the body or in a calorimeter. In the case of protein, however, the problem was somewhat more difficult for a part of the end products of protein combustion in the body is eliminated in the urine and feces and the latent heat thereby lost had to be subtracted from the heat value of protein as determined in the calorimeter.

In 1894 Rubner<sup>26</sup> constructed the first successful respiration calorimeter designed for the measurement of the gaseous exchange between a living organism and the atmosphere which surrounds it and the simultaneous measurement of the quantity of heat produced by that organism. By means of this apparatus Rubner verified the method of Pettenkofer and Voit of calculating the heat production (indirect calorimetry) and he proved that the law of conservation of energy held for the living organism.

It was not until 1905 that the respiration calorimeter was brought to a high degree of technical perfection by Atwater and Benedict.<sup>1</sup> With their apparatus it was possible to determine simultaneously with the measurement of the heat elimination, not only the carbon dioxide production, but also the oxygen consumption of the subject. Studies made by Benedict and his associates, at the Carnegie Nutrition Laboratory, using the perfected calorimeter, have added greatly to the exactness of our knowledge with regard to the metabolism in prolonged fasting,<sup>4</sup> the metabolism of normal persons,<sup>6</sup> of infants,<sup>8</sup> and of diabetics.<sup>7</sup> They also confirmed the agreement between direct and indirect calorimetry. Lusk<sup>18</sup> and Du Bois and their co-workers have likewise demonstrated, in a large series of pathologic conditions, the close agreement between the two methods. As a result of these investigations the use of such a complicated apparatus as the respiration calorimeter has been shown to be unnecessary for clinical work and that in its place the comparatively simple method of indirect calorimetry may be used.

Krogh,<sup>16</sup> of Copenhagen, and Carpenter,<sup>11</sup> of the Carnegie Nutrition Laboratory, have described and compared in great detail the various kinds of respiration apparatus used in indirect calorimetry. Carpenter has shown that for indirect determinations two types of apparatus are suitable, the closed circuit and the gasometer.

By far the best apparatus of the closed circuit type is the Benedict unit apparatus.<sup>2</sup> By means of a mask, mouth piece or nasal tubes, the subject rebreathes air from a closed system in which the carbon dioxid is absorbed by soda lime, and, as the oxygen is used up, it is replaced by oxygen in known amounts. The air within the apparatus is kept in constant circulation by means of a blower. A small spirometer is inserted in the circuit as an expansion chamber and volumetrically records the respiratory movements on a smoked drum. Knowing the weights of oxygen used and the carbon dioxid eliminated, one can readily calculate the heat production. As pointed out by Carpenter, this apparatus is very satisfactory and indeed the best for many purposes, especially when used in conjunction with a calorimeter or with the cot-chamber calorimeter described by Benedict and Tompkins.<sup>9</sup> We have found, however, that for clinical work the unit apparatus is rather cumbersome. It requires constant checking to see that it is absolutely air tight, for a leak of 20 or 30 c.c. during a fifteen minute determination will appreciably affect the result, because such a leak in this type of apparatus will be equivalent to the loss of so much oxygen and not equivalent to the loss of so much air as is the case in the gasometer method. Furthermore, the accumulation errors of the apparatus fall on the oxygen and not on the carbon dioxid determination, thus causing an error in the calculation of the respiratory quotient and heat production. The absorbing chemicals must be changed frequently and with the repairing and constant checking of the apparatus it is on the whole difficult to use in clinical work, particularly if many determinations are to be made.

The portable respiration apparatus recently devised by Benedict<sup>5</sup> for clinical work is a modification of his unit apparatus described above. It is designed primarily to give a rapid and at the same time a comparatively accurate measurement of the oxygen consumption without involving analyses or weighing. We have not adopted it as we prefer to determine not only the oxygen consumption, but also the carbon dioxid elimination since the heat production can thereby be more accurately calculated. Moreover, the difficulties inherent in the closed circuit type of apparatus are still present in the portable apparatus.

For clinical work the gasometer method introduced by Tissot<sup>29</sup> in 1904 is considered by us the most satisfactory. Briefly, the determinations are made in the following manner: A mask is adjusted over the

patient's mouth and nose and by means of expiratory and inspiratory valves the total volume of the patient's expired air is collected in a gasometer for a known period of approximately ten minutes. Duplicate determinations are made of the carbon dioxide and oxygen content of the expired air, the analyses being done in the Haldane gas analysis



FIG. 229.—Mask and connections showing valves and intake pipe.

apparatus.<sup>14</sup> Since the ventilation rate for each minute is known as well as the amount the carbon dioxide produced, and the oxygen absorbed, it is possible to calculate by means of calorie tables the total calories produced each hour.

The following points in the routine determination of the basal metabolic rate deserve further discussion: To obtain comparable results the patient must be in the postabsorptive condition, that is,

he must fast for at least twelve hours preceding the test. It is very important that this rule should be observed because all kinds of foods cause an increase in the heat production and this effect may not entirely disappear for twelve hours after their ingestion.<sup>28</sup> Moreover, the patient must be at complete rest and the effects of previous muscular exertion eliminated by requiring him to rest in bed for twenty minutes before the test is started for we have shown in a series of experiments that a test period of this length of time is quite sufficient to obtain the basal metabolism.<sup>11</sup> During the preliminary rest period an observer sits with the patient, noting at intervals the character and rate of the heart beat and the respiration; likewise, about the middle of the period, the blood pressures, both systolic and diastolic, are obtained. After twenty minutes' rest a mask is accurately adjusted over the nose and mouth of the patient and securely held in place by means of tapes so that there is no leakage of air around the mask (Fig. 229). A mask is preferable to either a mouthpiece or nasal tubes. With a little experience it is possible to adjust the mask so that it is not only comfortable for the patient, but also air-tight. One of the chief advantages of the gasometer method is that should a very slight leak of a few cubic centimeters occur around the mask during the course of an experiment the end result is not appreciably affected, while a leak of a similar volume in the closed circuit apparatus has a value at least five times as great, because in the latter case it is equivalent to the loss or gain of so much pure oxygen.

During the test proper the observer sits with the patient recording his pulse and respiration rates and noting and recording on a special chart any movements. Care is taken to impress the patient that even slight movements materially affect the test and it is almost always possible to obtain their complete co-operation. Sometimes, however, in an extremely nervous person, a basal rate cannot be obtained on the first test. Instead of repeating the determination the same day the patient is instructed to return the following morning for a second test. In such instances the rate will occasionally be ten points lower than that obtained the first time when the patient was unduly nervous and frightened about an unknown procedure.

The total volume of the expired air is collected in a gasometer (Fig. 230) over a known length of time. Unlike the work with the closed circuit apparatus no appreciable error is introduced by failing either to start or stop the experimental period at exactly the end of a



normal respiration, a difficult thing to do with accuracy in the case of patients who breathe irregularly. Samples of the expired air are then collected over mercury in sampling tubes and analyzed in duplicate for carbon dioxide and oxygen. Approximately 10 c.c. of expired air are



FIG. 230.—Movable gasometer.

transferred into the burette of the Haldane gas analysis apparatus (Fig. 231) and after adjusting certain levels the reading of the initial volume of the sample is made, reading to the nearest 0.001 c.c. The gas sample is then passed back and forth over a solution of dilute potash to absorb the carbon dioxide. The levels of the solution are again adjusted and a second reading of the volume of the remaining

gas in the burette made. The contraction in volume of the gas, due to the absorption of the carbon dioxide by the potash solution, divided by the original volume, gives the percentage of carbon dioxide in the expired air. In like manner the percentage of oxygen is determined, potassium pyrogallate solution being used as the absorbent for oxygen.

The gasometer method is particularly suitable for clinical work because each step in the procedure can be checked by a second assist-



FIG. 231.—Haldane gas analysis apparatus.

ant, reducing to a minimum the chance of technical errors. Although the method requires care and accuracy in every part of the procedure, it is possible to teach the technic to laboratory workers who have had no preliminary scientific training other than that obtained in a high school. The most difficult step in the procedure is the analysis of the expired air. This, however, we have found to be inconsiderable. Our assistants can obtain routinely duplicate analyses agreeing within 0.04 per cent for carbon dioxide and 0.06 per cent for oxygen, and they

are able also to take entire care of their gas analysis apparatus. The equipment necessary for this method is simple and inexpensive and when properly constructed is rarely out of order and, except for cleaning, requires very little mechanical care. Furthermore, the apparatus is free from the many mechanical difficulties inevitably inherent in a closed circuit system in which the air current is driven by an electric pump. In the metabolism laboratory at the Mayo Clinic we are averaging 30 cases a day and have developed a very definite and routine procedure which has decreased the chance of technical error to less than 1 per cent.\*

The calculation of the basal metabolic rate from the experimental data is very simple. Knowing the volume of air expired by the patient in a minute (the ventilation rate) and the percentage of carbon dioxide and oxygen in the expired air it is possible to calculate the volume of oxygen absorbed by the patient in one hour, as well as the corresponding amount of carbon dioxide produced. Since the respiratory quotient, that is, the ratio between the volume of carbon dioxide produced and the volume of oxygen absorbed, indicates the kind of food being burned at the time of the determination, and since by means of calorie tables the calorific value of one liter of oxygen absorbed by the body in the burning of these substances is known, the total heat production each hour can be calculated readily. The total number of calories must be divided by the surface area, a factor dependent on the patient's height and weight. The number of calories for each square meter of body surface each hour must then be compared with the normal standards of comparison which are dependent on the age and sex of the patient. For convenience basal metabolic rates are expressed in percentages of the normal and when the heat production is greater than the normal the percentage is plus, and when less than normal the percentage is minus.

A very important contribution was made by Du Bois<sup>12,13</sup> in determining the heat production in normal controls. Rubner<sup>24</sup> had suggested that the heat production of an individual is proportional to his surface area. For the determination of the surface area Meeh<sup>21</sup> proposed the formula: Surface area (in square centimeters) —  $12.3 \text{ (a constant)} \times \text{weight in grams.}^{26}$  However, using the surface area

\* The details of the technic are described in a laboratory manual by Boothby and Sandiford. The apparatus may be obtained from H. N. Elmer, 1186 Monadnock Building, Chicago.

obtained by this formula as a basis of comparison, the heat production of normal controls still showed quite wide variations, although not so great as when compared on the basis of weight alone. By exact measurements of the surface area of several bodies Du Bois demonstrated an error in the above formula due in greater part to the fact that the height of the subject was neglected. As a result of further studies Eugene F. Du Bois and Delafield Du Bois<sup>12,13</sup> devised a formula based on height and weight by means of which the surface area can be calculated with an average error of 1.7 per cent. This formula is:

$$A = W^{0.425} \times H^{0.725} \times 71.84$$

where A is the surface area in square centimeters, W is the weight in kilograms and H is the height in centimeters, and 71.84 is a constant. On the basis of this formula they then constructed a height-weight chart by means of which the surface area can be estimated at a glance. Du Bois<sup>12,13</sup>, using this new height-weight chart for the determination of the surface area in conjunction with his standards of normal basal metabolism with regard to age and sex, further showed that the metabolism of normal persons can be predicted with an accuracy of  $\pm 10$  per cent. This fact has been confirmed both by Means<sup>20</sup> and by Boothby<sup>19</sup>. Benedict<sup>3</sup> has severely criticized the method of predicting the heat production from the unit of surface area, maintaining "that the metabolism or heat output of the human body, even at rest, does not depend on Newton's law of cooling and, therefore, is not proportional to the body surface." Harris and Benedict<sup>15</sup> in a very exhaustive treatise have reconsidered the entire problem of the prediction of the normal basal metabolic rate and show that by proper biometric formulas based on stature, body weight, and age (the same factors used by Du Bois), "results as good as or better than those obtainable from the constant of basal metabolism per square meter of body surface can be obtained by biometric formulas involving no assumption concerning the derivation of surface area but based on direct physical measurements." Since their publication there has not been sufficient time to study in detail the fundamental accuracy of the two methods of prediction; we have, however, tabulated 404 determinations of the basal metabolic rate expressed in percentages above and below normal, using both the standards of Du Bois and of Harris and Benedict. The average rates of all the cases show that the rates obtained by

Harris and Benedict's method are 6.5 points higher than those obtained by Du Bois' method. The parallelism between the results obtained by the two methods is strikingly shown by the fact that 195 of the 404 determinations are within  $\pm 2.5$  of the average variation. Only 52 of the entire 404 rates deviate more than 7.5 from the average variation. The comparative agreement, therefore, of the two methods is very satisfactory, indicating as it does the similarity of both methods of comparison, and supporting in a high percentage of the cases the clinical conclusions based on the Du Bois and Du Bois height-weight chart and the Du Bois normal standards for comparison.

The metabolism laboratory at the Mayo Clinic was opened in March, 1917, by Boothby and Sandiford, under the clinical direction of Dr. H. S. Plummer, and in that year 1143 metabolic rates were determined on 549 patients. At that time the number of cases that could be studied in the laboratory in proportion to the number of thyroid cases at the clinic was relatively small. In consequence, considerable care was taken by Dr. Plummer to select typical cases of the various groups of thyroid disorders, and with his permission this analysis of the metabolic rates in the cases of exophthalmic goiter studied during 1917 is presented.

The determination of the basal metabolic rate is of the greatest value in thyroid disorders because it gives a very accurate mathematical index of the degree of functional activity of the thyroid gland. For example, in exophthalmic goiter the metabolic rate may rise well over 100 per cent above normal while in myxedema, with apparently complete cessation of thyroid activity, the rate falls to the region of 40 per cent below normal. In the milder cases of both groups the metabolic rate variations from the normal are proportionately smaller. On the other hand, beside thyroid disorders, there are no diseases that have so far been shown to have a constant and distinct variation from the normal in the basal metabolic rate except disorders of the pituitary gland, conditions of profound inanition, and fevers. However, an occasional case is met with in which there is a variation in the basal metabolic rate that cannot be explained or properly classified. Such variations are most frequent in patients with considerable nephritis or anemia. No definite instance of an increased basal metabolic rate has been found in that group of cases known as neurasthenia or chronic nervous exhaustion. The basal metabolic rate has proved, therefore, to be of great value in the differential diagnosis of neurosis simulating hyperthyroidism and true hyperthyroidism.

In 182 cases of exophthalmic goiter before any treatment was instituted the average metabolic rate was +51 per cent with an average pulse rate of 115. In 13 patients whose average metabolic rate, as outpatients, was +59 per cent with an average pulse rate of 115 the average metabolic rate fell to +46 per cent and the average pulse rate to 108 as a result of approximately one week's complete rest in bed. In 5 patients whose average metabolic rate, determined within two to five days after they entered the hospital, was +59 per cent and the pulse 118, after a further rest in bed of approximately one week's duration there was a definite improvement in their condition, as shown by a fall in the metabolic rate to an average of +48 per cent and pulse to 104.

The effect of a single ligation was studied in 16 cases. The basal metabolic rate taken after the patient had had several days' rest in bed and within five days before the first ligation was +54 per cent and the pulse 116. One week after the single ligation the average metabolic rate had decreased to +44 per cent and the pulse to 112.

The immediate result of any operative procedure in hyperthyroidism is to cause at first a rise in the metabolic rate for a few days, followed by a gradual fall to a distinctly lower average on the level than that obtained preceding the operation. The curve of the basal metabolic rate on the average roughly parallels the pulse rate curve. The former is, however, a far more accurate index of the degree of hyperthyroidism than is the pulse rate, as the latter shows more individual and extraneous variations, for example, the irregularities of auricular fibrillation.

The effect of the second ligation is likewise a general improvement in the patient's condition as evidenced by a decrease in the metabolic rate. An average figure of any value on the immediate result of the second ligation in the patients in the 1917 series cannot be given as practically no rates were obtained in the same case immediately preceding and following the second ligation. There is a very marked improvement in these patients when they return for their thyroidectomy two to four months after the second ligation. In 22 patients (Table 1) there was an average decrease in the basal metabolic rate from +46 per cent to +39 per cent and in the pulse from 115 to 107 with a gain in weight from 46.4 to 54.5 kg. in the determinations made a few days after the second ligation as compared with the data obtained after three months' rest at home and just previous to

thyroidectomy. From the clinical history it is probable that the basal metabolic rate determined at the time the patients returned for operation after having had two ligations and three months' rest at home may not necessarily represent in all cases the period of maximum improvement produced by the two ligations and rest. A definite improvement from thyroidectomy in those patients who had had two ligations and a three months' rest was shown two weeks following operation by a decrease in the basal metabolic rate from +39 per cent to +16 per cent and in the pulse rate from 107 to 89.

In another group of 19 patients (Table 2) with exophthalmic goiter in whom the preliminary basal metabolic rate varied between +13 per cent and +50 per cent, giving an average of +31 per cent with an average pulse rate of 104, and in whom a primary thyroidectomy was done without any other preliminary treatment, except for a short rest in bed, the basal metabolic rate fell, about two weeks after operation, to +5 per cent and the pulse to 84.

The general effect of the treatment adopted at the Mayo Clinic for severe cases of exophthalmic goiter may be illustrated, then, by the following data: In a group of 22 patients (Table 1) the average basal metabolic rate, before any treatment was instituted, was +66 per cent with a pulse rate of 123. As a result of rest in bed and two ligations the rate in these patients before they went home had decreased to +46 per cent and the pulse to 115. The further improvement that occurred from three months' rest at home reduced the average metabolic rate to +39 per cent and the pulse rate to 107, and finally, after thyroidectomy and just before the patients were discharged from the clinic, the rate was +16 per cent and the pulse 89.

As will be noted following thyroidectomy there is almost always a marked decrease in the basal metabolic rate within two weeks after the operation and, as a rule, there is still further improvement in the succeeding months, just as is seen to occur in the interval after the second ligation. Occasionally, a varying degree of hyperthyroidism may persist, as shown by an elevated basal metabolic rate. In these cases a second (and rarely a third) thyroidectomy is indicated.

TABLE 1.—THE EFFECT OF TWO LIGATIONS AND THYROIDECTOMY ON THE BASAL METABOLIC RATE IN EXOPHTHALMIC GOITER

Case	Before treatment			Within five to nine days after second ligation			Three months after second ligation			Ten to thirty days after thyroidectomy		
	Wt., kg.	Pulse	B. M. R., per cent	Wt., kg.	Pulse	B. M. R., per cent	Wt., kg.	Pulse	B. M. R., per cent	Wt., kg.	Pulse	B. M. R., per cent
208970	50.1	139	+101	38.1	118	+36	52.2	95	+50	56.8	69	+15
201022	48.5	175	+98	40.9	124	+49	51.5	114	+26	48.1	107	+6
196042	46.0	138	+93	45.6	126	+61	53.3	104	+43	51.9	91	+20
197894	46.7	128	+77	39.5	129	+46	58.4	113	+13	56.5	105	+1
192274	27.3	138	+76	40.1	120	+53	42.7	129	+58	40.9	92	+27
194824	42.4	127	+76	41.6	123	+58	51.9	110	+34	51.4	100	+13
210160	54.9	131	+75	57.7	124	+60	63.9	105	+55	63.0	82	+21
196845	49.7	129	+74	47.5	146	+78	55.3	129	+68	56.0	120	+68
215648	42.1	117	+73	43.4	115	+54	48.0	82	+12	53.7	74	-6
202677	60.5	98	+65	58.4	96	+34	64.1	94	+55	61.9	86	+34
191713	49.0	87	+65	43.5	83	+45	50.5	90	+62	50.5	71	+49
187927	48.5	121	+63	45.0	117	+43	49.4	112	+53	48.6	70	+3
189311	60.7	141	+60	49.9	88	+27	58.3	105	+43	56.0	44	0
199039	43.1	121	+56	36.6	123	+50	48.2	100	+50	48.6	76	+14
200063	46.5	95	+55	45.9	110	+58	46.9	121	+54	46.6	97	+20
199909	46.0	134	+55	46.0	127	+42	52.8	132	+52	53.0	88	+13
136490	55.1	107	+55	44.2	104	+41	65.5	82	+11	65.3	85	0
194306	43.2	126	+53	42.0	124	+48	50.1	117	+21	49.5	105	+9
197356	58.5	99	+52	53.0	80	+13	60.0	77	+1	56.9	75	-2
191257	60.5	130	+50	56.7	123	+45	61.2	110	+34	58.5	117	+16
209717	55.6	133	+47	54.0	141	+37	59.0	127	+39	57.0	88	+16
190576	53.0	86	+31	51.6	92	+31	55.6	106	+25	58.3	106	+19
Average....	49.5	123	+66	46.4	115	+46	54.5	107	+39	54.0	89	+16



TABLE 2.—THE EFFECT OF PRIMARY THYROIDECTOMY ON THE BASAL METABOLIC RATE IN EXOPHTHALMIC GOITER

Case	Preliminary before treatment		About two weeks after operation	
	Pulse	B. M. R., per cent	Pulse	B. M. R., per cent.
214581	88	+50	70	+19
196806	109	+45	93	+ 3
202992	107	+45	92	+ 5
200219	145	+42	115	+12
201229	102	+40	75	+14
202481	105	+39	68	+ 1
202527	112	+36	92	+15
194686	97	+35	75	+ 1
212298	108	+34	91	+ 5
202232	113	+32	118	+32
203326	127	+30	89	+10
3396	101	+29	83	+13
198725	99	+27	67	0
196664	79	+21	58	-11
203291	87	+18	73	- 6
199740	95	+18	69	- 7
217150	99	+16	85	- 5
215895	118	+16	98	- 9
208637	89	+13	84	+ 6
Average.....	104	+31	84	+ 5

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## TUBERCULOSIS OF THE THYROID\*

W. A. PLUMMER AND A. C. BRODERS

The literature on tuberculosis of the thyroid may be divided into three classes: (1) Reports of isolated cases usually of the so-called primary type, in a number of which the clinical picture and pathologic appearance of the gland had been modified by secondary infection and abscess formation; (2) descriptions of the histologic findings in thyroids obtained in routine necropsies in persons having died of general miliary tuberculosis; and (3) studies based on reviews of the pathology of simple and exophthalmic goiters.

Reports such as those of Fraenkel in which tuberculosis of the thyroid was said to have been demonstrated in all except six of 580 necropsies following deaths from general miliary tuberculosis are of value, but clinicians are especially interested in reports based on pathologic material from persons who have had definite goiters or who have complained of symptoms due directly or indirectly to thyroid disease.

Ruppner, in 1908, reported 3 cases of colloid goiter in which he had demonstrated areas of tuberculosis. von Werdt, in 1911, found tuberculosis in one gland in 28 cases of exophthalmic goiter, and in three glands in 444 cases of simple goiter. Mosiman, in 1917, reviewed the literature and reported 9 cases in which operation had been performed in the Crile Clinic. The glands in 5 cases which had been previously diagnosed exophthalmic goiter also showed hyperplasia. In the goiter of one of 2 patients who had been designated as having had mild or questionable exophthalmic goiter were hyperplastic areas; one patient who had had hypertension, and another, sarcoma of the thyroid did not show hyperplasia.

Mosiman's admirable report brought out the striking relationship between hyperthyroidism and tuberculosis of the thyroid. This association is evidently not a coincidence; either a hypertrophic gland is rendered more susceptible to invasion by the tuberculosis bacillus or

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the infection stimulates the parenchyma to an abnormal activity and is thus indirectly responsible for the hyperthyroidism with its attendant symptoms. Although the great majority of hypertrophic thyroids are not tuberculous, any infection which may even in a few instances be an etiologic factor is of interest in dealing with a disease the cause of which is so shrouded in mystery.

Few, if any, of the cases of tuberculosis of the thyroid which have been reported were diagnosed previous to the microscopic examination of the glands. The condition was not suspected in any of our cases previous to operation, and their study was pursued in the hope that some evidence might be gained which would indicate whether or not the hypertrophy was secondary to the tuberculous infection, and also with a view to determining, if possible, any diagnostic points which in the future might lead us at least to suspect the condition previous to or at the time of operation. In using the term hypertrophy we refer to the cell hypertrophy, that is, the transition of the normal cuboidal to the columnar type of epithelial cell.

We shall report briefly 7 cases that have been under observation in the Mayo Clinic. A full discussion of the symptoms and findings will not come within the limits of this paper. For convenience these cases are divided into three groups: (1) Cases with high degree of hyperthyroidism, (2) cases with a moderate degree of hyperthyroidism, and (3) cases in which hyperthyroidism was mild or absent.

Case 1 (Group 1).—This patient had had general symptoms for four years, but no local symptoms. The thyroid gland was diffusely enlarged and slightly nodular, but not unusually hard. There was no tenderness to pressure. Bruits and thrills were present. The basal metabolic rate was +48. A clinical diagnosis was made of exophthalmic goiter, with the degree of severity 3 on a scale of 1 to 4. At operation the gland was thought to be hypertrophic with multiple adenomas. The pathologic examination revealed scattered areas of tuberculosis, a slight amount of fibrosis, some round cell infiltration, and extensive parenchymatous hypertrophy.

Case 2 (Group 1).—This patient had been conscious of the goiter for eight months; symptoms had been noted for ten months. The basal metabolic rate was +87. The thyroid gland was slightly enlarged with the granular "feel" of a hypertrophic condition. Bruits and thrills were present. The clinical diagnosis was exophthalmic goiter, degree of severity 3. At operation both lobes were found to

be about two and one-half times normal in size and had the appearance of an ordinary hypertrophic gland. The pathologic findings were the same as those in Case 1.

Case 1 (Group 2).—The goiter had been diagnosed by the family physician six months before. General symptoms had been noted for two years; there were no local symptoms. The thyroid gland was about normal in size; it had no nodules but was unusually hard for a hypertrophic gland. The basal metabolic rate was +26. Exophthalmic goiter was diagnosed, the degree of severity 2. A normal sized gland which appeared to be hypertrophic was found at operation. Extensive tuberculosis, a moderate amount of fibrosis and round cell infiltration, and a fair degree of parenchymatous hypertrophy were found on pathologic examination.

Case 1 (Group 3).—The general symptoms in this case had been present for one year; no thyroid enlargement and no local symptoms had been noted. The patient's neck was short and fleshy, and, except for a hard nodule on the left side about 1.2 or 1.8 cm. in diameter, neither lobe of the thyroid could be palpated. The isthmus was palpable and unusually hard. The basal metabolic rate was +21. The diagnosis was definite hyperthyroidism, with degree of severity 1. The condition was considered unusual and thought to be exophthalmic goiter or thyrotoxic adenoma. The gland was found firmly adherent to all the surrounding structures, muscles, fascia, and trachea. Very little bleeding occurred during the removal of the gland which indicated an old inflammatory condition. In cutting across the gland the surgeon found a large amount of scar tissue. The pathologist reported extensive tuberculosis, marked fibrosis, round cell infiltration, slight parenchymatous hypertrophy, and great destruction of the gland.

Case 2 (Group 3).—Four months before this patient's examination enlargement of the right lobe had been noticed. General symptoms had probably existed for one year; there were no local symptoms. The thyroid had the contour of a normal gland, although about three times its normal size; it was hard, and slightly nodular. The basal metabolic rate was +21. A tentative diagnosis was made of mild hyperthyroidism, with degree of severity 1, probably exophthalmic goiter, possibly carcinoma of the thyroid. At operation the gland was found to be hard and resembled carcinoma, but was believed to be some form of infection throughout the gland. As in Case 1 of Group 3, the patho-

logic examination revealed extensive tuberculosis, marked fibrosis, round cell infiltration, slight parenchymatous hypertrophy, and extensive destruction of the gland.

Case 3 (Group 3).—The general symptoms had probably been present for two years. The patient complained of pressure in the throat. A very hard tumor in the left lobe of the thyroid was not sensitive to pressure; no bruits were heard in the thyroid vessels. The metabolic rate was not determined. A diagnosis was made of neurasthenia with a possible thyrotoxicosis from an adenoma. Because of the density of the tumor, carcinoma of the thyroid was also considered. Examination of the gland removed at operation showed degeneration and inflammation. The only normal tissue remaining was that in the pyramidal lobe. The surgeons were suspicious of malignancy. The pathologist discovered about the same amount of tuberculous destruction as in Cases 1 and 2 of this group, but more parenchymatous hypertrophy.

Case 4 (Group 3). In this case enlargement of the right lobe of the thyroid had been noticed for one month. Three weeks before examination the left side had begun to enlarge. A neurasthenic syndrome had been present for years. The lobes were not greatly enlarged, but were very hard; a small nodule could be palpated in each. A clinical diagnosis was made of a small adenoma of the thyroid, possibly carcinoma, because of the recent developments and extreme hardness of the gland. At operation a small hard tumor pressing on the trachea was found. The surgeons were unable to exclude malignancy, but considered the condition inflammatory. The pathologic findings were practically the same as in the other cases in Group 3, although there was more destruction and fibrosis, and no parenchymatous hypertrophy.

The 2 cases in Group 1 represent typical high grade exophthalmic goiters. Before operation the glands were believed to be ordinary hypertrophic thyroids. The surgeon did not detect any unusual condition. The pathologist reported extensive parenchymatous hypertrophy with tuberculosis in scattered areas.

The single case in Group 2 represents an intermediate stage. This was a case of typical exophthalmic goiter, but with a less severe degree of hyperthyroidism. The surgeon apparently did not consider it more than an ordinary hypertrophic gland. The pathologist

reported a fair degree of parenchymatous hypertrophy, also very extensive tuberculous involvement.

In all but one of the cases in Group 3 the thyroids were smaller than those in Group 1. The glands were hard, somewhat fixed, and nodular; two of them had grown rapidly. The clinician had recognized an unusual condition in all, and had suspected carcinoma in three. In the first 2 cases the definite evidence of a mild degree of hyperthyroidism was confirmed by basal metabolic rates. The last 2 patients were examined before we had the means of estimating the basal metabolism; however, hyperthyroidism had been suspected in the first of these; in the last case no mention was made of the possibility of hyperthyroidism. The parenchyma of the gland was so completely destroyed that the diagnosis of the absence of hyperthyroidism made at that time was probably correct. The striking point in the cases is that 5 of the patients, probably 6, were suffering from hyperthyroidism. The greater the tuberculous involvement the less severe the toxic symptoms. This may be explained by the more extensive destruction of the gland.

In 2 of the 5 patients with definite hyperthyroidism the goiter was noticed before the symptoms; in 2 the opposite was true, and in one no thyroid enlargement had been discovered. In these findings there is nothing decisive to indicate that tuberculosis preceded the hyperthyroidism. Even had we had a larger series it is doubtful whether definite conclusions could have been reached, as such tuberculous processes would undoubtedly have been progressing for months before the enlargements could have been noticed. The symptom in these cases are so insidious that the time of the onset of the condition is difficult to determine. Probably all cases of tuberculosis of the thyroid are secondary to some process elsewhere in the body. In this series if such foci were present they were too small to have any clinical significance; evidence of active tuberculosis elsewhere in the body could not be demonstrated on critical examination.

In Case 2 of Group 3 definite evidence of myxedema appeared at the end of two months. This condition has also been noticed in cases of simple chronic thyroiditis following operations. It is questionable whether the usual amount of thyroid tissue should be extirpated when the gland is inflammatory because of the possibility of a resulting hypothyroidism caused by the subsequent destruction of the remaining

parenchyma. Cases of the type placed in Group 1 cannot be distinguished from ordinary exophthalmic goiter.

In cases similar to those placed in Group 3, the condition may at least be suspected before operation. Carcinoma of the thyroid may be associated with hyperthyroidism, but the growth is usually more nodular and is not so apt to involve the entire gland without causing a much larger tumor. Chronic simple thyroiditis may give the same thyroid signs as tuberculosis, but in our experience it has not been associated with hyperthyroidism. Sarcoma of the thyroid is a rare condition, and we have never had a case of actinomycosis.

Three of our patients were operated on too recently to give us any definite information as to the ultimate prognosis following operation but they have all been benefited. One patient had myxedema. One is in perfect health two years following operation. The other 2 have not been heard from recently.

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## THE SELECTION OF OPERATION FOR EXOPHTHALMIC GOITER\*

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Surgery, at the present time, gives a higher percentage of cures than any other measure in the treatment of exophthalmic goiter. For a number of years the mortality following surgical procedures has gradually decreased, largely because much has been learned regarding the selection of the type of operation which is safest in any given case, and because the greater number of patients are operated on earlier in the course of the disease than formerly, and at a time when they are better surgical risks. It is possible by present day methods to operate in large number of consecutive case of exophthalmic goiter without a death. There are, however, a few patients who fail to respond to pre-operative medical treatment and who must be subjected to operation at a relatively high risk in order to offer a chance for cure. Refusal to operate in this group of cases naturally diminishes the death rate. On the other hand, poor judgment in selecting the type of operation which is best and safest in a given case, and in advising operation in certain cases that are non-surgical at the time, increases the mortality.

If the disease is left to run a normal course it progresses in several different ways. In a few instances the onset is sudden, with rapid development of symptoms, and the progress is so quick that the patient soon becomes a poor surgical risk. In the greater proportion of patients, however, the onset of the disease is so gradual that in its incipency it can scarcely be recognized save by one highly experienced in the diagnosis of hyperthyroidism. In such patients the symptoms gradually increase in number and severity and an enlargement the thyroid gland occurs. As a rule the disease reaches its height during the second six months of its course and the patient passes through a period which usually is referred to as a crisis. During such periods all the symptoms become markedly exaggerated; the pulse rate is

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high, there is rapid emaciation and weight loss with extreme nervousness and mental irritability, and oftentimes vomiting and diarrhea; marked damage occurs to the vital organs, such as the heart, liver and kidneys. Unless the disease proves fatal, the majority of patients improve greatly after a period of from one to several weeks, although as a rule they are never so well after having passed through a crisis as they were before. The amelioration of symptoms may persist for a period varying from a few months to several years, but in the majority of patients a second or even a third crisis eventually develops. With each crisis the damage to vital organs, especially the heart, liver, and kidneys increases, until the patient finally suffers more from the symptoms produced by these degenerative changes than from the disease itself. In a third but small group of patients the disease runs a chronic course from its onset, without the development of acute crises.

Fortunately and unfortunately patients improve when treated medically; fortunately, because patients unfit for surgical treatment may improve to such an extent that they become fairly good surgical risks; and unfortunately, because a knowledge of the fact that improvement occurs under medical treatment leads many practitioners to use medical measures only in the management of exophthalmic goiter, apparently without fully realizing the sad state to which a large percentage of the patients thus treated will ultimately be reduced. Many patients who have been treated medically for a long period apply for surgical aid and are found to have such marked degenerative changes in their vital organs that it is impossible for surgery to effect a cure. Operation usually stops the progress of the disease even in this stage, but the damage to the vital organs cannot be repaired; it would be quite as reasonable to expect to cure patients with well pronounced central nervous system lesions from tertiary syphilis by means of anti-syphilitic treatment.

It is often a perplexing problem to decide just how toxic a given patient is and how much damage has been produced by the disease, and for these reasons it is difficult to decide what operative procedures the patient will safely endure. Although the mortality is largely affected by the decision, no absolute rules can be given as to the selection of the best type of operation; each case must be judged on its own merits. A condition which in one patient would justify the performance of a thyroidectomy, in another patient would be counter-

balanced by some other factor that would make the operation dangerous. There seems to be no way of elucidating all the possible conditions that may arise, as these can be recognized only by observers who are highly experienced in dealing with patients with exophthalmic goiter.

In operating in such cases in the Mayo Clinic certain factors are taken into consideration in selecting the type of operation. The ideal surgical procedure in exophthalmic goiter is partial thyroidectomy as soon as the first symptoms of the disease appear and it can be definitely proved, by metabolic tests, that hyperthyroidism is present. At this stage of the disease a primary thyroidectomy can usually be performed with a very low death rate, and many such patients are restored to normal health. The percentage of patients operated on during the early stage of the disease is steadily increasing, and an increase in the percentage of cures will result.

It cannot be denied that certain patients improve and apparently recover under medical treatment. However, in the beginning of the disease it is impossible to distinguish between the patients who may fall in this group and those who are destined to become severely damaged as the disease progresses. A great responsibility is assumed, therefore, by advising medical treatment in early cases, in which thyroidectomy might prevent the severe conditions, and in many instances the death of patients who would fail to improve under medical treatment.

The metabolic rate is a definite index to the degrees of hyperthyroidism in a given patient at a given time. It is of very great value as a diagnostic aid in the early stages of exophthalmic goiter when studied in conjunction with the symptoms and general appearance of the patient. As a rule, the clinical picture presented by the patient, the metabolic rate, and the pulse pressure run hand in hand, the symptoms increasing and decreasing as the metabolic rate varies. However, patients do not always present the same clinical picture while carrying similar metabolic rates; for instance, one patient with a rate of +50 per cent may be extremely sick and in a crisis, while another with the same rate may show a very different clinical picture and be a fair surgical risk. Some persons seem to develop a certain tolerance to increased metabolism. We occasionally see a patient who, while carrying a certain metabolic rate, must be classified as a bad surgical risk. Later, this same patient, while carrying the same rate,

may present a different clinical picture and stand the operation which previously was considered unsafe. In all instances in which a high metabolic rate is associated with symptoms indicative of a high grade toxemia, such as nervousness, irritability, cardiac dilatation, high pulse rate, loss of weight and strength, nausea, vomiting and diarrhea, the condition must be looked on as serious and non-surgical. The metabolic rate gives no indication of the amount of damage which may have been done previously; it can be used only partially as a means of deciding on the best type of operation to perform. We make a careful selection of the type of operation for patients with a rate above +40 per cent, and we hesitate to perform a primary thyroidectomy in patients with metabolic rates 60 to 70 per cent above normal. In the majority of such patients without marked cardiac damage, and who except for this high rate would seem good risks, we perform a preliminary ligation as a means of testing the ability of the patient to stand any operative procedure without the precipitation of an acute hyperthyroidism. If a mild reaction follows the ligation, a thyroidectomy is performed after seven or eight days, but if the reaction is severe, it is best to do a second ligation and to wait three or four months before performing a thyroidectomy.

Certain patients, after having had the disease for some months, present themselves for treatment because of increased symptoms. As a rule they have lost weight and probably are losing weight at the time. Such patients will usually be found to have high metabolic rates. If the loss of weight and general strength has been marked, and especially if the patients are highly nervous and irritable, we have found that a thyroidectomy is performed with considerable risk in these cases because a crisis may be precipitated by even a slight surgical procedure. In such instances we usually perform two superior polar ligations, under local anesthesia, at one operation or at intervals of seven or eight days, and wait for three or four months before performing a thyroidectomy.

Patients who consult us during acute crises are considered extremely dangerous surgical risks, and we prefer to treat them by means of rest, fluids, and careful nursing until the crisis is passed, and there is a gain in weight, with a corresponding subsidence of the pulse rate, the nervousness, and mental irritability. The metabolic rate usually drops considerably following a crisis; therefore, patients who have just passed such a period are not likely to be thrown into an acute

hyperthyroidism by a thyroidectomy, but on account of the marked degenerative changes in their vital organs and the weak, degenerated heart muscles, the operation may prove a dangerous procedure. In such patients we have usually found it safer to perform two superior polar ligations, under local anesthesia, seven or eight days apart, thus preparing the way for thyroidectomy several months later.

In a few patients who seem to be risks for any surgical procedure and who fail to respond to medical treatment sufficiently to warrant an operation, we occasionally are able to perform two ligations at intervals of from seven to eight days after having made one or two injections of quinin and urea solution, or of hot water into the thyroid gland. Such injections seem to lessen the tendency to excessive reaction following ligation.

It will be noted that ligation is performed with two ideas in view; first, as a means of testing patients who seem fit surgical risks for thyroidectomy but concerning whom there is enough doubt to make ligation the safer procedure, and second, as a means of preparing patients for thyroidectomy.

Patients who are being tested and who stand a ligation well, can, in the majority of instances, stand a thyroidectomy. The reaction following the ligation of one superior pole, performed under local anesthesia, is similar to, but much less marked, than that which occurs when a thyroidectomy, instead of a ligation, is done. This reaction consists of an increase in the pulse rate and temperature, vomiting, nervousness, and mental irritability; it usually begins within a few hours after the operation has been performed, gradually increases and reaches its height within from thirty-six to forty-eight hours. In exceptional cases it may be so marked as to produce death from an acute hyperthyroidism in from one to four days following operation. As a rule, however, it begins to subside after from forty-eight to seventy-two hours and, in a few days, the patient is in a state similar to that present before the operation was performed. In cases in which the reaction following such a ligation is marked we perform a second ligation, and later a thyroidectomy.

When ligation is done with an idea of preparing patients for thyroidectomy, the superior pole is ligated on each side, under local anesthesia, at intervals of seven or eight days, and the patient is allowed to wait for three or four months before a thyroidectomy is done. During this period there is usually a marked abatement of symptoms, an increase

in weight averaging about 21 pounds for each patient, and the general improvement is such that a thyroidectomy may be done with comparative safety. As a matter of fact, in some of these cases the surgeon hesitates to recommend a thyroidectomy, but experience has shown that hyperthyroidism may recur in from one to five years unless a thyroidectomy is done.

The degree of improvement which follows thyroidectomy depends largely on the amount of damage to the vital organs at the time of operation and the amount of thyroid tissue which is removed. If the damage to organs has been extensive it is impossible to restore the patient to normal health; the operation usually stops the hyperthyroidism and great improvement follows, but the organs do not return to normal. In doing a thyroidectomy on a patient with exophthalmic goiter we have found that in order to bring the metabolic rate to nearly normal it is necessary to remove all of one lobe, the isthmus, and the greater portion of the other lobe, leaving a piece of gland tissue probably not larger than one-half or one-third of a normal sized lobe. If not enough thyroid tissue is removed, and this may be proved by metabolic tests, the patient may be benefited, but will continue to have symptoms of hyperthyroidism. In a few patients the remaining portion of the thyroid gland hypertrophies and the symptoms recur. In either case, if the metabolic rate indicates a degree of hyperthyroidism which seems incompatible with good health, we re-operate and remove a portion of the thyroid tissue which was left at the first operation.

## TETANY IN THE EUNUCHOID. REPORT OF A CASE\*

H. W. WOLTMAN

While the degree of dysfunction of the thyroid gland can now be established with mathematical precision by determining the rate of metabolism, disorders of the parathyroids usually progress unrecognized until in the adult, at least, the symptoms of tetany suddenly become manifest. That these are dependent on a hypofunction of the parathyroid glands seems now firmly established. A condition of hyperparathyroidism, analogous to that of hyperthyroidism, has never been demonstrated anatomically; that it may exist, clinically, in the guise of certain peculiar nervous diseases of obscure or wholly unknown etiology as, for example, myasthenia gravis or periodic family paralysis, has been a matter of supposition, although proofs that will satisfy scientific criteria are still lacking.

There remains no longer any doubt that tetany, spasmophilia, carpopedal spasm, arthrogryposis, and so forth, are but different designations of the same disease, which is dependent on a substratum of parathyroid deficiency, regardless of the immediate exciting factor. While it is likely that Hippocrates already knew of the disease, it appears to have been recognized first in children in modern times by Clark, who, in 1815 described a condition of laryngospasm associated with cramps in the hands. In 1817 Johnson proposed the term carpopedal spasm. In the adult, it was first described by Steinheim in 1830, and independently by Dance in 1831, in a scholarly work, under the title "*LeTetanos Intermittente*." To Dance is usually ascribed the credit of priority. Then followed a long list of French works, and in 1852 the disease received the name of "*Tetanie*" from Corvisart.

The next significant advance in our knowledge of this malady was made by Sandstrom, a Swedish anatomist, who in 1880 discovered the glandulæ parathyroidæ, although others, particularly Virchow, in 1864, had often noted "accessory thyroids" of pea-size, located behind

\* Reprinted from *Jour. Nerv. and Ment. Dis.*, 1919, 1, 433-448.

the body of the thyroid. Following this, in 1881, Nathan Weiss made the observation that tetany often followed total thyroidectomy. These two findings, however, were not correlated until about 1895 when it was shown that the parathyroids were developmentally and anatomically entirely independent from the thyroid. On the physiologic side, their independence was demonstrated by Vassale and Generale, Biedl, Pineles, and others, the first two writers pointing out for the first time the causal relation between clinical tetany and the parathyroid bodies.

Because of certain unusual features and its relation to endocrine disorders of another source the following case seems worthy of a detailed report.

Case A228896. E. H., aged 36, a barber, presented himself at the clinic for examination April 19, 1918, complaining of convulsions.

*Family history.*—His father had died at the age of seventy of carcinoma of the rectum; his mother was living and in good health, save for some cardiac trouble, at the age of sixty-nine. In her younger days, she frequently had attacks of very severe, supra-orbital headaches suggesting migraine. Two brothers are living; one, forty years of age had had attacks of localized edema for two years, which appeared at times on the legs, the trunk, the scalp, and the face. Swelling of the eyelids sufficient temporarily to shut off vision frequently resulted. While this usually followed a localized and continued pressure, it sometimes appeared suddenly without known cause and vanished as suddenly. There was no itching. We had no opportunity of observing this brother; however, the description certainly suggests an angioneurotic disturbance, possibly a Quincke's edema. He also suffered considerably from periodic headaches. Another brother, aged 26, had croup as a baby and is now afflicted with some stomach disorder associated with vomiting. A third brother died in infancy of spasms lasting three to four days. Four sisters are living; one has rheumatism; two died at the age of one year, the one of measles associated with convulsions, the other from an unknown cause.

*Personal history.*—The patient had had general convulsions which began at the age of one year, and disappeared spontaneously at the age of two years. From the fourteenth to the sixteenth year he had inflammation of the bowels associated with vomiting. The vomiting spells continued until he was 21 when a herniotomy and an appendectomy were performed; after this he was perfectly well for a period



of eight years. He then married. His wife is well but she has never been pregnant. The patient's appetite is variable and his bowels are constipated. He sleeps fairly well, uses tobacco and coffee in moderation, and alcohol semi-occasionally and in very small amounts. Save for an occasional attack of tonsillitis and la grippe, he has enjoyed fairly good health until the onset of the present trouble. About seven years before examination, while working in the barber shop, he noticed that his legs became very easily tired; this was particularly marked on Saturday nights, following a long day's work, and it became progressively worse. Three years previously he noted that his abdomen became distended at intervals of about a week, the distention being so marked as to render breathing uncomfortable; this lasted about three quarters of an hour, and was accompanied by eructations of gas. There appeared to be no relationship to meals and there was no intestinal upset save some constipation. The condition persisted until the occurrence of convulsions, similar in nature but less severe than those described subsequently. After three or four attacks of this character, while on his way home from work one Saturday night he lost control of his legs; they began to jerk up "like a horse with the spring-halt." He summoned help, and with assistance walked about 10 feet farther when his legs stiffened out and he was compelled to stagger along on his tip toes, which he accomplished only with the greatest effort. Ultimately he fell and was carried home and put to bed. His general condition improved sufficiently to enable him to be up off and on but he could not work.

In the fall of 1915, the spasms appeared with increasing intensity and frequency, as many as five or six a day. During this time he had attacks that caused his jaw to cramp, as though yawning, the mouth remaining wide open for from thirty to forty minutes at a time. On other occasions a trismus appeared which was so marked that a diagnosis of tetanus was entertained and anti-tetanic serum administered. He seemingly improved somewhat but had to remain in bed almost constantly for eight and a half months, on account of spasms in his arms and legs. The convulsions diminished in frequency, appearing about once a week, and in January, 1916, the patient was able to get about with the aid of crutches. Convalescence was protracted and incomplete; his legs began swelling and by August of 1916 they had become two or three times their normal size; he had also edema of the abdominal wall, the back, and probably some ascites. His face was

not swollen. In September he developed prickling and numbness of the hands and a burning pain in the legs which rapidly became excruciating and he felt as though his legs were being "roasted over a fire." The slightest noise disturbed him greatly and he became very irritable. One afternoon he suddenly cried out, rolled over on his left side, lost consciousness, and turned a livid color (laryngospasm?), saliva running from his mouth. There was no general convulsion. He remained unconscious for three days, at the end of which time he became greatly agitated, was noisy, scolded everyone in sight, and accused them of turning fire on his legs. One day he decided to go to his sister's home for dinner, where he thought they were celebrating a wedding anniversary. After just having finished a meal, he wanted to eat again, saying he had had nothing since the previous day. He recognized persons, and seemed to be oriented as to place. He complained bitterly of the burning, prickling, and numbness of the fingers. His legs had been straight before he lost consciousness, but were now flexed at the knees at an angle of about 45 degrees, which position they maintained in spite of efforts made to correct the deformity. The tendons, particularly those of the hamstring muscles, seemed to have become shortened. The patient was so reduced in flesh that one's fingers could easily be placed around his thighs, although the latter did not seem disproportionately atrophied. His face had a puffed-out appearance and he was almost completely bald. The skin was dry and scaly "like a fish." The abdomen was covered with brown pigmented spots from an eighth of an inch to one inch in diameter. In October improvement began; the mental condition cleared up and the spasms diminished both in number and in intensity so that he had but five or six from then until the time of his examination. For fifteen months, however, he had been bed-fast, and every attempt to get him up was promptly followed by vomiting.

*Physical examination.*—The patient was well developed, somewhat emaciated, lying in bed with his thighs flexed on the abdomen and his legs flexed on his thighs at an angle of about 45 degrees. He appeared to be about six or seven years older than his actual age. His face had a puffy appearance, was much wrinkled, and of a pasty yellowish-gray color. The skin of the trunk was moist, somewhat boggy to the touch, and free from pigmentation. The panniculus adiposus was moderately reduced in thickness and normal in distribution except for a well-developed mons veneris. The hair was of a light

brown color, thin, and rather dry. Very few hairs were present in the axillæ and about the genitalia. The latter presented the transverse distribution of the female type. A well-developed mons veneris was present. The penis was somewhat smaller than normal; the left testicle was very small, about 1 by 0.5 cm., and the right was missing, having been removed seven years previously when it had become the site of a tumor of unknown type. There was practically no hair on the rest of the trunk or extremities.

Mentally, the patient was clear and alert, though his speech was very deliberate. The voice was cracked and higher in pitch than the average. Examination revealed a slight gingivitis; the teeth showed no transverse grooving nor other trophic disturbances; the tonsils were somewhat enlarged and contained a few plugs; there was pharyngitis marginalis on the left side; anterior deflection of the septum to the left and a high posterior deflection to the right; the membranæ tympani were slightly retracted; the superficial glands were normal to palpation; the palpation of the thyroid gland was uncertain; the heart and lungs were normal; there was a linear scar over the right inguinal region, the site of a former herniotomy; the liver, kidneys, spleen, pelvis, rectum, and spine were normal. The systolic blood pressure was 135 mm. and the diastolic 92 mm. The urine was examined on four different occasions, once following a convulsion. The amounts were normal, the specific gravity varied from 1012 to 1025, the reaction was acid, with a trace of albumin, and an occasional pus cell in three specimens, and once a few red cells; there was no sugar. March 19 the blood showed 76 per cent hemoglobin, 5,100,000 red blood cells, 15,600 white blood cells, and April 16 it showed 75 per cent hemoglobin, 4,400,000 red blood cells, and 9,200 white blood cells. A test meal given April 4 showed the gastric contents to be cream colored, with advanced chymification, total acidity 40, free hydrochloric acid 20, no lactic acid, no blood. The x-ray examination of the stomach was negative. The Wassermann tests of the blood and of the spinal fluid were negative. X-rays of the sella and hands were negative. On two occasions examinations of the stool showed a few red blood cells, no parasites. Skin tests, made by Dr. Fricke-Davis, were found negative to proteose, oats, corn, cabbage, tomato, lactalbumin, walnut, egg-white, egg yolk, casein, strawberry, veal, horse serum, cat dander, horse dander, lamb, bran, *Staphylococcus aureus*, and ragweed.

A combined phenolsulphonephthalein test showed an output of 40 per cent in two hours.

Neurologic examination showed the cranial nerves to be negative save for a pallor of the nerve-heads, suggesting a slight primary optic atrophy; the musculature presented a marked general atrophy; the small muscles of the hands and the calves were perhaps disproportionately affected. There was bilateral pes cavus. While the knees could be completely flexed, extension beyond an angle of 45 degrees was prevented by contracted hamstrings. Tonus was about normal throughout. Fibrillary twitchings were occasionally noted in the interossei of the hands. There was marked general weakness and almost complete loss of power in the thighs. The calves imparted a leathery sensation to palpation. There was no reaction of degeneration in any of the atrophied muscles. The biceps, triceps, supinator, and abdominal reflexes were normal. The left patellar reflex was normal, the right moderately increased. The left tendo achillis was slightly more active than normal, the right greatly increased. Ankle clonus was present on the right side. The plantar response on the right side was extensor by the methods of Babinski, Chaddock, and Rossolimo, while that on the left was constantly flexor. Sensation for touch, pain, and temperature was normal throughout, save over the dorsum of the toes where tactile sensibility was possibly slightly reduced. Vibration and joint sensibility were normal. Tendon sensibility seemed to be almost absent in the legs. Coördination was very slightly impaired in the arms; that of the legs, making allowance for weakness, was probably normal. The bladder and rectal control was good.

A Chvostek II was readily elicited. On compressing the left upper arm in testing for the Trousseau phenomenon, the fingers grew pale and cold, and within approximately half a minute passed into a tonic spasm in marked abduction and extension. The spasm extended rapidly up the arm and almost simultaneously appeared in the right arm, in the muscles at the floor of the mouth, in the tongue, in the lips, and to some extent in the legs. The fingers were maintained in almost constant tetanic extension and were widely abducted, the wrist and elbow being flexed. Off and on, there appeared clonic convulsive movements of the brachial abductors and internal rotators. The position of the fingers shifted slowly from time to time with occasional slight flexion of the distal phalanges, particularly those on the ulnar side. The

lips were at times drawn tensely over the teeth, and at times assumed a sucking position; the lateral angles were approximated into the "fish mouth." The patient stated that this drawing of the lips over the teeth was occasionally so intense that bleeding resulted. The mandibular muscles also partook in the attack, the jaw being fixed by a tonic spasm, sometimes closed, sometimes opened, and interrupted occasionally by clonic lateral movements, which were very painful. Consciousness remained clear throughout and the patient was able to speak whenever the muscles of articulation were not too actively involved in the spasm. The attack was terminated after about sixty-five minutes by the administration of one-half grain of morphin; the spasm gradually disappeared, leaving the fingers last. The spasm was at times obviously very painful, and left the patient greatly exhausted but unable to sleep. At no time did he exhibit any emotional outbreaks. Elevation of the arm above the head did not bring on the characteristic hand attitude, Alexander's test, nor did a pedal spasm appear when the extended leg was flexed on the abdomen, Schlesinger's phenomenon. Erb's test, utilizing the external peroneal nerve, gave the following electrical values:

K.C.C.*	A.C.C.	A.O.C.	K.C.Te.
0.6	1.8	1.2	3. MA.

When the dorsum of the tongue was lightly tapped, a small welt appeared which gradually subsided, Schultze's phenomenon. Tapping the N. peroneus externus was followed by a dorsal flexion and abduction of the foot, phenomenon of Lust.

Hoffmann's test, which makes use of the hyperexcitability of the sensory components of peripheral nerves, gave the following formula where S = sensation, O = local, ↓ = radiating, P = persistent, K = cathodal, and C = closure.

\* It may be stated that in infants, with the exclusion of certain organic conditions as hydrocephalus, spastic paraplegia, cerebral sclerosis, and the presence of a K.O.C. of less than five milliamperes indicate tetany, Thiersch's phenomenon. This arbitrary rule does not apply to adults in whom normally the electrical values are relatively much lower. This change takes place after the second or third year and is already established at 12-13, as Holmes has shown. The normal values at these ages are as follows:

	C.C.C.	A.C.C.	A.O.C.	C.O.C.	Chvostek present in
2 to 3 years.....	2.5	4.2	4.3	5.0	5 per cent.
12 to 13 years.....	1.7	3.6	2.3	5.0	20 per cent.

K.O.C. is equivalent to K.C. Te. as the former cannot always be obtained.

	O.K.C.S.*	K.C.P.S.	A.C.S.	A.C.P.S.	K.C.↓
Cutaneous branch, peroneal.....	0.1	0.2	0.12	0.3	1.4
Cutaneous branch, postradial .....	0.2	0.8	0.14	1.0	3.0
Supra orbital.....	0.08	0.2	0.18	0.5	0.6

The temperature remained normal throughout, save twice when it rose to 99. This elevation was not preceded nor accompanied by convulsions. The pulse rate averaged about 70, and varied only slightly during the attacks. May 8 the attack appeared first in the muscles of the throat and continued for forty minutes. In the course of this seizure the *m. flexor pollicis brevis* of the left hand stood out as a prominent narrow band, while the neighboring muscles were comparatively relaxed. Two or three times the respiratory muscles were involved in a spasm of half a minute's duration. The eyeballs were turned upward until the cornea could hardly be seen, and could not be rotated downward until the spasm had subsided. This attack was preceded from four to five hours by a burning sensation in the pit of the stomach.

May 12. This spasm resembled the others; it began in the eyelids, and was of one hour and five minutes' duration.

May 15. In this attack, which was of one hour and fifteen minutes' duration; the right leg showed both tonic and clonic spasms. They were, however, transient. The face and eyeballs were involved also.

Medication did not produce the desired results, which is quite in keeping with the general experience in this type of tetany. Thyroid did not seem to alter the course of the disease one way or the other; any change, in fact, seemed for the worse. Calcium lactate was administered during a greater part of the time while the patient was under observation. The striking results so often seen in the tetany of infants were not noted; absolutely no change in the course of the disease could be observed. The intravenous administration was not tried. A communication from the wife states that the patient vomited considerably, had numerous convulsions, and ultimately died March 3, greatly emaciated.

While tetany is decidedly rare in this country, as Griffith has

\* These findings, while of interest from an academic standpoint, require too great a reliance on the statements of the patient and his intelligent coöperation to gain great prominence as a diagnostic procedure.

pointed out, isolated cases are probably more common than is ordinarily supposed. The diagnosis, when the patient is seen during an attack, may be made with tolerable certainty at a glance. The physician, however, usually does not witness the attack itself, and it is only by bearing in mind the existence of such a disease that serious blunders can be averted. The story of tingling and stiffness in the fingers which the patient relates to the physician is usually hearkened to with customary tolerance, attributed to the fantasy of the individual, and dismissed as "nervousness."

Clinically the most outstanding feature of tetany is the well-known tonic spasm of the hands and arms resulting in the characteristic "writing position," or the "main d'accoucheur" as Trousseau ably described it. While this is typical, all other positions of the fingers may be taken. At times clonic movements are associated with the tonic, as in our case. Rather characteristic is the onset and association of the spasm with parasthesias, especially formication in the hands and feet, burning, a sense of mummification or drawing. The cramps themselves may or may not be painful. Next in frequency to the extremities is involvement of the facial muscles.

Ocular spasms were noted in 7 of 122 cases by von Frankl-Hochwart. The eyes may suddenly become set or may move independently. Occasionally, there is a spasm of the pupillary and ciliary muscles. Spasms of the tongue, noted in our case, are decidedly rare. Laryngospasm, so common in infants, is rare in adults, but may occasionally prove fatal. Muscles of the trunk may participate. The bladder is said never to be involved and the gastro-intestinal tract probably not, as the work of Wilson, Stearns and Janney goes to show. At times the respiratory muscles, both of the chest and diaphragm, are involved and rarely is there cardiac stillstand. Spasm of the bronchioles has been described by Lederer and may simulate pneumonia.

Retention of consciousness is a characteristic feature, although general convulsions with loss of consciousness may occur. The duration of the attacks varies from several seconds to several days, and they may be bilateral or unilateral. Involvement of the legs alone is rare; it has never been observed by von Frankl-Hochwart.

Vasomotor disturbances are not uncommonly seen. Thus in 10 per cent of cases, one sees the rather characteristic swollen "tetany face" which may persist long after the active tetany has subsided. Redness or pallor of the extremities may be noted. Chloasma,

pemphigus, herpes, urticaria, dermatitis exfoliativa, localized edema resembling a Quinke's edema, marked dermatographia, sweating, polyuria, and transient glycosuria occur. There are often trophic disturbances of widely varying types, among them, falling of the hair, brittleness of the nails, transverse grooving of the teeth—a valuable sign of early tetany—cataract formation, especially in tetany of maternity, and even necrosis of the fingers as in Raynaud's disease. Occasionally, there is optic atrophy.

While the mentality is generally clear, psychic disturbances may be seen, usually of the type of intoxication deliria (Kraepelin) with confusion and hallucinations. There may be fears, increased excitability, insomnia, lack of attention, memory defects, and impaired intellectual accomplishments, but seldom a marked grade of dementia. At times, psychic disturbances suggesting a psychic equivalent may replace or accompany the attacks.

The association of epilepsy with tetany is of great interest. In infancy, as is well known, tetany frequently expresses itself in general epileptiform convulsions. In adults this is rare unless associated with other expressions of the disease. Here the epilepsy may accompany a typical attack of tetany, the patient retaining the characteristic tetany attitude of the arms and legs; it may immediately precede it, follow it, alternate with it, or it may exist as an entirely independent affection. This type of epilepsy does not respond to bromid treatment and pursues its course *pari passu* with that of the tetany itself. The fact that typical epileptiform seizures have been produced in parathyroidectomized rats, cats, and apes is significant; as in the human, they are especially prone to occur in the young. As demonstrated by Ibrahim, Falta and Kahn, hyperexcitability to mechanical and particularly chemical stimulation, for example, adrenalin and pilocarpin, obtains also in the vegetative nervous system, indicating the deep-seated physiologic action of the parathyroid glands.

Characteristic as the clinical features of tetany are, just so indefinite are the pathologic changes noted in the parathyroids or elsewhere at necropsy. Constant findings are as well as missing. *Per contra*, pathologic changes, particularly tumors, have been found in the parathyroids in cases which showed no evidence of tetany (Benjamins, MacCallum, Askanazy, Weichselbaum, and others). This, however, may be explained by the vicarious functioning of the remaining parathyroids, it having been demonstrated that two



of the four glands ordinarily suffice to prevent the occurrence of tetany. Findings elsewhere in the body are usually irrelevant or entirely missing.

The intimate anatomic relationship of the parathyroid glands to the thyroid seemed for a long time, *per se*, to stand in the way of arriving at the underlying cause of tetany. Even after it was established that both ontogenetically and morphologically the parathyroids are independent structures, these organs could not be dissociated in the minds of investigators, a fact which accounted for the first theory of parathyroid function, namely that of Vassale and Generale, who looked on the parathyroids as furnishing a secretion, the purpose of which was to neutralize a toxin secreted by the thyroid gland. In the light of subsequent developments, however, this assumption had to be abandoned.

The occurrence of tetany among certain classes of workers, especially shoemakers, tailors, and so forth, that is, the idiopathic variety, in whom the epidemic-endemic character and seasonal variation is particularly prominent, implies certain conditions which current theories fall short in explaining. Oppenheim's suggestion that some toxin may be present in the working material of these persons commands serious thought as it could also explain the endemic character, the presence of several cases in the same family, the frequent rise in temperature, and the association with an hallucinatory confusion as the common type of psychosis in this disease. Wermel's experience in Moscow in 1901, where he observed among 26 rubber washers working in a small quarter of a factory 7 cases of tetany within a very short time, while of 700 workers in other parts of the factory not one single instance of tetany occurred, may be considered evidence in favor of Oppenheim's theory.

The endeavor to identify more definitely the chemical nature of the substance at work has met with more or less success. Fuchs considered tetany a mitigated form of chronic ergotism. The most active principal of ergot, according to Biedl, B-imidazolylæthylamin, an amino base, and an end product of protein metabolism, is looked on by some to be the chemical substance; however, experimental poisoning with this material does not produce the full picture of tetany. According to Eppinger, an injection of 5 gm. histidin chlorhydrate in persons with intestinal disorders will bring about a Chvostek phenomenon, a positive Trousseau, and increased galvanic excitability.

The association of tetany and rickets in infants, artificially fed, had long been noted. Thus attention was directed toward the metabolism of calcium, and the work of MacCallum and Voegtlin gave the problem a new direction. These authors found a marked deficiency of calcium in the blood of patients with tetany as well as a marked increase in the excretion of calcium in the urine, a condition which might be termed "calcium diabetes," analogous to the excretion of dextrose following extirpation of the pancreas. The marked beneficial effect of feeding calcium in spasmophilia supports this view. The inactivation of circulating calcium by intravenous injections of trisodic citrate was followed by convulsions similar to those occurring in tetany, which are relieved by the administration of calcium. Quest also showed diminished calcium content in the brains of three spasmophilic infants, although these findings have been challenged by other investigators. The parathyroids are accordingly considered the regulating mechanism of calcium metabolism. Certain objections to this theory have been raised. It was pointed out that bleeding followed by replacement of the fluid lost, by saline, relieved the convulsions, instead of increasing them, by reason of having further reduced the calcium content by one-third; that the bones surely contain enough calcium to delay, at least, the onset of tetany following parathyroidectomy, which is not the case; and that animals ultimately die within the same period of time regardless of whether calcium has been administered or not. Strontium and magnesium also control the attacks.

Certain other factors which have a definite bearing on the disease remain to be explained. It has long been noted that feeding meat hastens the onset and increases the intensity of the convulsions. A large increase of the ammonia content in the blood, or an alkalosis, preceding the onset of the convulsions, and a definite acidosis following, have been noted. The problem was further investigated by Wilson, Stearns, Janney and others, and its bearing on protein metabolism studied. It was demonstrated that the injection of ammonia into healthy animals in the same amounts noted in animals with tetany was in itself sufficient to produce convulsions, although these were of a different character.

The more recent findings which give promise of leading finally to the solution of the chemical aspects of the problem are centered around the guanidin bases. It remains necessary to correlate these with such definite factors as calcium metabolism, magnesium and phosphorous

excretion, and age. This Koch has attempted to do and his theory may be briefly summarized:

Guanidin and its alkylated compounds, as methyl and dimethyl-guanidin, are known to be very toxic substances, capable of producing exactly the symptoms seen in tetany. This base has been shown by Burns and Sharpe to be present in the urine of normal dogs to the extent of 1 mg. per 1000 c.c., and after parathyroidectomy, 8.7 mg. per 1000 c.c.; the blood contains normally 0.25 mg., and following parathyroidectomy 1.1 mg. It is known that meat diet increases the severity of the tetany, and that a high protein diet produces large quantities of ammonium which generally unite with carbon dioxide to form the innocuous substance urea or with other acids to form salts. Here, however, the ammonium, which is increased to the point of tetany, unites with the cyanimids, forming the alkali guanidins until the threshold dose of guanidin intoxication is reached, when tetany results. The attendant lactic acid formation permits ammonium to join the acid radicals, prevents the formation of poisonous guanidins, and by hydration converts the poisonous cyanimids into non-poisonous urea. Thus the tetany serves as a detoxication mechanism. The mother substance of guanidin is supposed to be methylcyanimid, which Koch isolated from the urine of parathyroidectomized dogs in small quantities as the picolonate and as the picolonate of its polymer trimethyl-melamin, both of which, by adding ammonium, are readily converted into the guanidins. The apparent beneficial effect of the calcium is produced by interfering with the normal balance of monovalent and bivalent cations, which control the colloidal relation of water and lipoids of the cell membrane, an excess of the former producing lipid in a water phase, which increases the permeability of the cell, thus enhancing intracellular activity and quickening the cellular metabolism by facilitating the removal of waste products by adding the bivalent calcium, it changes the protoplasmic colloidal relation from lipid in a water phase to the dispersion of water medium in a lipid phase. This depresses cellular metabolism, prevents the entrance of the toxic guanidin bases into the cell body and thus delays the appearance of the toxic symptoms. When the guanidin concentration rises too high, however, intoxication results unless so much calcium is administered that cellular exchanges are practically prohibited and death results.

A subject of interest is the theory in which tetany is considered in

the light of an anaphylaxis. In our case there was no such sensitization. The theory has many shortcomings. Tetany has also been considered a deficiency disease, dependent on vitamin disturbance.

Whatever the chemical mechanism may be there remains to explain, if possible, the origin of the parathyroid insufficiency itself in our particular case, in which there was a definite endocrin syndrome present. The relation of the parathyroids to the other members of the hormone system was everywhere apparent. The history of convulsions and laryngospasm in various members of the family during childhood at once commands attention. The family history of migraine and the development in a brother of a condition which strongly suggests an angioneurotic, or Quincke's edema, assumes new significance. The abnormal dryness and scaling of the skin, suggesting thyroidal features, and the marked pigmentation noted during one of the exacerbations, possibly of adrenal origin, are striking indeed. There is, finally, the direct evidence of disturbance of the gonads in the development of a testicular tumor, with the clinical picture designated variously as pseudohermaphroditism, eunuchoidism, "infantilisme reversif ou tardif" of Gandy, pointing to disturbance of the secretory activity of the cells of Leydig.

Of these designations, Falta prefers the term eunuchoidism, since infantilism would imply an arrested sexual life, absence or only partial development of secondary sexual characteristics, faulty involution of the lymphatic apparatus, delayed growth and ossification, child-like dimensions, depending on closure of the epiphyses, and mentality, which are not present in these cases.

It was largely through the work of Claude and Gougerot that the intimate hormonal relation of these organs was shown, the sum total of the disorder produced being termed by them "insuffisance pluri-glandulaire endocrinienne". While this term has been criticized as abandoning more or less the effort to determine what particular glands are most extensively or solely involved, it serves to impress on one the intimate correlation, not hormonal antagonism, of the entire endocrine system, injury of one member being reflected by a perverted action of all the other ductless glands due to a shifting of the chemical coördination.

This observation is supported on the anatomo-pathologic side by the demonstration in a number of these cases of a multiple endocrine sclerosis (Falta) underlying which we have, as shown by Wiesel, Falta,

and others, a connective tissue diathesis, the expression of a primary constitutional defect. On the basis of this we note a peculiar locus of lessened resistance exposing these organs to attack by noxious substances which would ordinarily not result in any such serious consequences. It is quite possible indeed that such diseases as chronic lenticular degeneration, which are associated with hepatic cirrhosis belong in this category, as organs showing insufficiency have a marked tendency to sclerosis.

I wish not to be misunderstood as implying that all of these cases exhibiting multiple glandular involvement are associated with this sclerotic process, for this is obviously incorrect; I do believe, however, that it is very important to distinguish the type of case in which tetany merely appears secondarily as a result of this shifting of chemical co-ordination due to a primary involvement of one or the other members of the endocrine system, and the other type in which all of the glands of internal secretion are primarily involved with or without sclerosis on the basis of a constitutional hypoplasia. This distinction can probably be made in a large percentage of cases. The prognostic significance is apparent. In the first instance, return to normal of the primarily involved gland will be accompanied by a restitution of the remaining organs; in the second case, the outlook must necessarily be much more unfavorable.

The outcome in other cases of tetany likewise differs materially with the type. Thus, in the idiopathic or artisan's variety, death is almost unheard of; however, in this type, as well as in tetany of maternity, only one-fifth of all patients may be said to recover completely. Four-fifths are more or less permanently invalided and a large percentage die of tuberculosis. Of subsequent complaints which these patients have may be mentioned cramps, tremors, sensation of drawing in the limbs, general fatigability with weakness, paresthesias, headache, vertigo, sleeplessness, fears, and increased lability of affect. The chronicity of the disease may be illustrated by one of von Frankl-Hochwart's patients, who showed repeated exacerbations for sixty-six years.

In gastric tetany, the mortality rate varies from 50 to 75.5 per cent. In the tetany of infancy the mortality, according to Potpeschnigg, is over 23 per cent. According to Guleke the prognosis of post-operative tetany is not good, 25 per cent of the patients dying, and

17 per cent developing a chronic or markedly recurrent tetany. The mortality in pregnant women, according to Seitz, amounts to 7 per cent.

Tetany associated with eunuchoidism appears to be decidedly uncommon, as a survey of the literature reveals. Phelps reported a case of tetany occurring in combination with psychic developmental deficiency, infantilism, early optic atrophy, cataract, and trophic disturbances of the teeth. A case described by Falta in a seventeen year old male showed tetany, epileptiform seizures, pallor, dry skin, myxedema, and infantilism. It is quite impossible to arrive at an idea as to the ultimate outcome of the few cases referred to, as examination is made without subsequent note.

In concluding, it must be emphasized that tetany is by no means to be regarded an illness of little significance. It would seem justifiable to assume that when marked evidence of polyglandular participation appears, in which the disorder is not initiated by a disturbance of the thyroid gland, the prognosis is rendered much more grave, for, after all is said and done, the therapeutic results from gland administration other than thyroid leaves much to be desired. A distinct heredo-familial tendency to glandular disturbance would render the prognosis even less favorable, judging from somewhat analogous situations recognized in dealing, for example, with the psychoses or certain neurasthenic states. Further evidence bearing on this question is needed and would be of considerable value in aiding in the solution of a problem having such fundamental bearings.

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## THE EFFECT OF SPLENECTOMY ON THE THYMUS\*

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Probably very few glands in the body have been the subject of as much barren research as the spleen and thymus and but few positive statements can be made with regard to the function of either of the glands. They do not appear to be necessary for life and their loss produces little demonstrable change, which may be the reason we know so little about their functions.

Both the glands are lymphoid in character; from clinical and experimental standpoints this is believed to establish a definite relationship between them. A few deaths have been reported which seemed to have some connection with a large thymus and atrophic spleen (Avellis). The investigators of the thymus have been more insistent on a relationship between the two organs than the investigators of the spleen. Friedleben seems to have been the first to hint that such a relationship exists. In Basch's experiments the removal of the spleen in a thymectomized animal did not produce any effect. Klose claimed that the spleen is the principle compensatory organ of the thymus. He found that the spleen, at first much enlarged after thymectomy, later seemed to undergo functional atrophy; its removal in some of the thymectomized animals produced death. Klose and Vogt assumed that the adult spleen undertakes the function of the thymus when the latter regresses and suggested that the thymus compensates for the spleen when the latter is removed. Soli found the weight of the spleen in chickens and rabbits unaffected by thymectomy. Lucien and Parisot also found the weight of the spleen unchanged after thymectomy, but in certain cases they observed an increase in the number and the size of follicles. Perrier found an increase in the lymphatic tissue of the spleen and the presence of very large germinating centers in the follicles after thymectomy. Magnini claimed there is a hypertrophy of the spleen in both young and adult rats after thymec-

\* Reprinted from *Endocrinology*, 1919, iii, 299-306.

tomy. Matti found primary hyperplasia followed by atrophy of the spleen after thymectomy; he also reported hyperplasia of the thymus following splenectomy in the dog. Bayer stated that there is a mutual compensation between the spleen and the thymus. If the spleen is removed the function of the thymus becomes more efficient; if the thymus is removed the spleen becomes more active. Pappenheimer, in his careful study of the effect of early extirpation of the thymus in rats, was not able to detect any alteration in the spleen. Many other studies have been made on the effect of thymectomy or splenectomy in various species of animals such as guinea pigs,<sup>12</sup> rats,<sup>17</sup> dogs,<sup>16, 8, 13</sup> but little or no mention has been made of the thymus. This brief review of the pertinent literature shows that the so-called pluri-glandular theory has been applied to the spleen and thymus with the usual lack of discrimination and substantial data.

In my series of experiments on animals from which the spleen had been removed for various purposes the thymus was observed regularly. As nothing definite was determined, although some suggestive material was obtained, a special series of experiments was performed for the specific purpose of determining whether or not splenectomy produces any effect on the thymus. Observations on the thymus after removal of the spleen have been made on both adult and very young animals of several species. Since the thymus regresses and almost disappears early in life it would seem that should any effect of removal of the spleen be demonstrable, the splenectomy would have to be performed on very young animals. The spleen was therefore removed from young animals just as soon as they were considered able to withstand the operation successfully. One or more members of the same litter or of the same age were kept as controls. In some instances one of a litter was killed and the thymus removed and weighed at the time of operation and beginning observations of the animal used in the experiment.

All operations were performed under anesthesia, with sterile technic. The young animals were placed in an incubator immediately after operation because their temperature controlling mechanisms were not very stable. Many of the animals died from intercurrent disease but enough data were secured to justify certain conclusions. At necropsy a careful examination for thymic tissue was made and when any was found it was fixed in Zenker's solution without acetic acid and weighed twenty-four hours after fixation. Since the tissue

removed frequently consisted mainly or wholly of fat it was necessary to make several sections of the specimen in order to estimate the amount of thymic tissue present. The position of the thymus or thymic tissue varies with different species of animals. In instances in which no thymic tissue could be found grossly in the thorax and the neck, a histologic search was seldom made because small amounts of thymic tissue may usually be found microscopically in the normal adult animals.

Observations were made on 25 adult dogs from which the spleens had been removed at different periods varying from a few weeks to two years. The thymus of these animals did not differ from that of normal dogs. In a very few animals of the series a small amount of thymic tissue could be found, but in most instances it could not be noted grossly. The same variability in the amount of thymic tissue may be observed in normal adult dogs.

The spleens were removed from 16 puppies ranging in age from three to six weeks. Thirteen puppies belonging to the same litters were kept as controls. As is often the case, distemper killed most of the puppies within a short time after observations were begun, but a few of them lived several weeks and one lived eleven months after splenectomy. No difference in the thymic tissue of the splenectomized puppies and of their controls was noted although a great variability in the amount was found in the different animals, even of the same litter. One puppy would have a large thymus while another of the same litter would have only a trace of thymic tissue. No grossly discernible thymic tissue was found at necropsy in the splenectomized puppy that lived for eleven months after operation.

A few kittens were used in the investigation; no conclusions could be drawn. The kittens were found to have practically no thymus by the time they were old enough to be operated on safely.

Observations were made on 75 adult rabbits from which the spleen had been removed at different periods varying from a few days to two years. Very rarely was any thymic tissue found and, when found, the amount was small. With one exception the splenectomized rabbits did not have more thymic tissue than the controls.

Spleens were removed from 21 young rabbits ranging in age from five to nine weeks. Twelve rabbits belonging to the same litters were kept as controls. Great variation in the size of the thymus was found even in the animals of the same litters. Splenectomy did not cause an

TABLE 1.—SALIENT DATA OF THE MOST IMPORTANT EXPERIMENTS PERFORMED ON GOATS

Goat	Sex	Age at time of operation, days	Weight at time of operation, kg.	Operation	Time from operation to necropsy, days	Weight at time of death, kg.	Weight of thymus, gm.	Estimated amount of thymic tissue in mass weighed, per cent
77	M	25	5.0	Splenectomy	318	15.5	0.9	20
78	M	25	5.2	Splenectomy	327	15.9	1.0	50
79	F	25	5.6	Splenectomy	490	16.5	0.9	50
80	F	25	5.1	Control	483	23.0	0.85	35
81	M	25	4.9	Splenectomy	174	24.0	1.6	90
82	F	25	5.4	Control	490	14.5	1.52	75
83	M	28	4.9	Splenectomy	9	3.15	3.3	85
84	M	28	4.8	Control	18	4.0	3.9	85

increase in the thymus, however, nor apparently any earlier regression of the organ.

In observations made on a large series of normal adult goats only a small amount, if any, thymic tissue could be recognized grossly. However, at necropsy of a very old goat (Goat 50) from which the spleen had been removed in another experiment a large thymus was found. This seems to indicate that the lack of the spleen might be a cause of the enlargement of the thymus although the experiment was complicated by other factors, such as the administration of cholesterolin, and the x-ray. Accordingly several careful experiments were carried out on young goats. Normal data were obtained from goats of various ages that had been used in other experiments, and it was found that the size of the thymus varied greatly.

The spleens were removed from eight kids slightly less than a month old. Four kids of the same age were kept as controls and the thymuses of a few other kids that died shortly after birth were studied for controls. At birth and during the first few weeks of life the thymus is usually quite large, but even at this age individual variation is marked. Most of the kids withstood splenectomy well, then died or were killed at various periods of time after operation. A careful

review of the results does not show any difference in the thymus of the splenectomized animals and that of the controls (Table 1 and protocols of goats).

An attempt was made by microscopic study not only to estimate the amount of thymic tissue in relation to the fat, but also to gauge the possible activity of the gland from its general appearance, number of Hasall's corpuscles, and so forth. Decided variations were found but there was no evidence that splenectomy produced any specific change.

Luckhardt has made some suggestive observations with regard to splenectomy in very young rabbits and dogs.<sup>8</sup> Tachigara and Takagi apparently did not note much difference between the effects of splenectomy in the puppy and in the adult dog. Our results show that some animals from which the spleen has been removed quite early in life develop in the same manner as the unoperated controls; furthermore, no definite specific change in the development due to the loss of the spleen was observed in any of the animals. Most of the splenectomized animals died before the controls died, however, and under the same conditions that the controls were developing normally. While removal of the spleen in the young did not produce any noteworthy change in development it seemed to make the animal less able to withstand the stress of life. In order to obviate the possibility of false conclusions owing to this individual variability in the thymus it might be of value to perform the experiments on rats as that species has been carefully standardized. It should also be remembered that since rarely some effect of splenectomy has been noted on other tissues, such as the bone marrow and lymph nodes, it is possible that a larger series of experiments might have contained one or more that were positive.

#### PROTOCOLS

*Goat 50.*—A very old female angora goat weighing 98.8 kg. was admitted to the laboratory Sept. 15, 1916, and was used by Dr. Luden in making cholesterol observations. Jan. 5, 1917, the spleen was removed successfully. Complete healing followed slight infection of the abdominal wound. Beginning February 26 the animal was given cholesterin and a few x-ray treatments. She gave birth to a kid April 17 and died June 17 at which time she weighed 36 kg. At necropsy a large thymus (4 gm.) was found. Histologically the thymic

tissue appeared to be very active; approximately 90 per cent of the tissue weighed was thymic.

*Goat 79.*—A female angora goat, one month old, weighing 5.6 kg., was splenectomized March 22, 1918. The weight of the spleen was 20 gm. The animal recovered from the operation and remained in excellent condition. It was allowed to run with its mother on pasture where it seemed to grow and develop normally. At the end of four months the animal did not differ noticeably from the controls. It weighed 18.2 kg. at this time. February, 1919, when the animal was returned to the laboratory, it weighed 22 kg. A series of blood counts and hemoglobin estimations were made; all counts fell within the normal limits. The animal lost some weight in the laboratory; May 25 it weighed 21.3 kg., but it remained in good condition until June, by which time its weight had decreased to 16.5 kg. This loss of weight was attributed to the loss of its hair which had been sheared and to the confinement in the laboratory, since the control also lost weight under the same circumstances. The animal was killed by bleeding under ether, and necropsy (300) was performed immediately after death; except for emaciation the animal was normal. The operative wound was healed perfectly; there were no adhesions. A small amount of thymic tissue was found. This was fixed in Zenker's solution without acetic acid and twenty-four hours after fixation it weighed 900 mg. Microscopic examination showed that about 50 per cent of the weighed tissue was thymic. There were many Hassall's corpuscles; the hemolymph nodes were undoubtedly greatly increased in this animal.

*Goat 82.*—A female angora goat one month old was splenectomized March 22, 1918. The kid was allowed to run with its mother on pasture where it developed normally. August 1 its weight was 20 kg.; February, 1919, it was returned to the laboratory weighing 24 kg. A series of blood counts and hemoglobin estimations was made; all counts were normal. The animal lost slightly in weight in the laboratory but remained in good condition until June 25 when its weight had decreased to 14.5 kg. One month before the animal had weighed 29.5 kg. The loss of weight was attributed to the loss of hair which had been sheared and to the confinement in the laboratory. The animal was killed by bleeding under ether. Necropsy (301) was performed immediately. The animal was emaciated but perfectly normal. A small amount of thymic tissue was found and fixed in Zenker's solution without acetic acid; twenty-four hours after fixation it weighed

1520 mg. Microscopic examination showed about 75 per cent of the weighed tissue to be thymic. There were but few Hassall's corpuscles. There were practically no hemolymph nodes; a few, measuring 2 mm. in diameter, were with difficulty found for microscopic study.

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## **HEART**





## AURICULAR FIBRILLATION AND LIFE EXPECTANCY\*

F. A. WILLIUS

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The most important and most frequent disorder of cardiac rhythm is that due to fibrillation of the auricles. Its presence in varying degrees of heart disease renders a prognosis exceedingly difficult at times. Prognosis in heart disease of course cannot be based on one factor but must result from the sum-total of evidence, subjective and objective, and from knowledge gained by adjunct methods.

Cardiac efficiency is determined by the integrity of the myocardium, especially of the ventricular myocardium, as life is dependent directly on the function of these chambers. Other cardiac defects are factors largely modifying the true issue.

As yet, no method of precision is known for determining cardiac efficiency, but the cardiovascular response to effort is probably the most satisfactory. The obvious objection to this method is personal equation which materially influences interpretations.

In dealing with an issue as uncertain as life is at best, no physician can conscientiously tell a patient that he will live a specified number of years, months, or days. The object of this study is not to advocate such dogmatism but to corroborate clinical impressions with statistics.

The present analysis is based on 500 cases of auricular fibrillation in which electrocardiographic examinations have been made at the Mayo Clinic. The cases of fibrillation in which electrocardiographic examinations were not made are not included for reasons of group standardization. This series covers a period of four and one-half years. The cases have been grouped for comparative study, and while the classification is not without certain objections its employment is quite satisfactory. The statistics are tabulated in Tables 1 to 32.

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Group A—Complete series of 500 cases of auricular fibrillation.

Group B<sub>1</sub>—Uncomplicated auricular fibrillation.

Group B<sub>2</sub>—Auricular fibrillation with premature ventricular contractions.

Group B<sub>3</sub>—Auricular fibrillation with arborization block.

Group B<sub>4</sub>—Auricular fibrillation with arborization block and premature ventricular contractions.

The groups complicated by arborization (impaired intraventricular conduction) include only those cases in which the ventricular conduction system was diffusely involved, as expressed by the presence of abnormal ventricular complexes in all three derivations of the electrocardiogram. In a previous publication<sup>2</sup> I have emphasized the gravity of this disorder unattended by abnormalities.

Group C comprises chronic valvular disease, grouped with reference to type of lesion. The criteria adopted for the diagnosis of mitral stenosis in the presence of auricular fibrillation are those laid down by Mackenzie, namely, the presence of a diminuendo apical murmur, diastolic in time.

Group C<sub>1</sub>—Auricular fibrillation in mitral insufficiency.

Group C<sub>2</sub>—Auricular fibrillation in mitral stenosis.

Group C<sub>3</sub>—Auricular fibrillation in double mitral lesion (insufficiency and stenosis).

Group C<sub>4</sub>—Auricular fibrillation in aortic insufficiency.

Group D includes disease of the myocardium, chronic myocarditis in the strict sense of a chronic inflammatory process, and myocardial degenerations secondary to other conditions.

Group D<sub>1</sub>—Auricular fibrillation in chronic myocarditis.

Group D<sub>2</sub>—Auricular fibrillation in myocardial disease secondary to hypertension with and without clinical nephritis.

Group D<sub>3</sub>—Auricular fibrillation in myocardial disease secondary to exophthalmic goiter (hyperplastic toxic).

Group D<sub>4</sub>—Auricular fibrillation in myocardial disease secondary to thyrotoxic adenomas (non-hyperplastic toxic).

Control series to all groups are compiled, corresponding in total number, occurrence by decades, and sex. The patients comprising series all received electrocardiographic examinations. An attempt was made to make the control series a just comparison; it seemed best, therefore, to exclude the graver forms of heart disease, namely, angina pectoris, arborization block, and lesions of the auriculoventricular bundle, aortic disease, and auricular flutter.

A  
AURICULAR FIBRILLATION—COMPLETE SERIES

Decade	Total	Patients heard from up to present time	Males	Females	Im- proved	Worse	Un- changed	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death	Average time
											Shortest time	Longest time
11-20	5	2	1	2	0	1	1					3 yrs. 5 mos.
21-30	37	29	19	10	3	6	6	162*			6 days	2 yrs. 4 mos.
31-40	79	58	28	30	9	12	8	262		z Tuberculosis y Pneumonia z Influenza		1 yr. 2 mos.
41-50	129	104	46	58	29	25	13	372		z ? y Pneumonia	13 days	11 mos.
51-60	158	126	63	63	28	30	23	452		z Apoplexy y ? z ?	3 days	11 mos.
61-70	77	58	35	23	2	15	7	342		z Cerebral hemorrhage y Pneumonia z Cholangitis	8 days	10½ mos.
71-80	15	14	11	3	0	0	3	112		z Cancer of the tongue y Cancer of the thyroid z Pneumonia y Diabetes z Peritonitis	15 days	11 mos.
Total ...	500	392	203	189	71	89	59	173 19	41.3	z Cancer of the cardia y Cancer of the stomach z Uremia	4 days	11 mos.
								.154 cardiac			8 days	2 yrs. 8 mos.
												1 yr. 3 mos.

\* Each letter refers to a single death other than cardiac.

A  
CONTROL SERIES

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of changed	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
11-20	5	4	1	3	2	2	0	0					
11-20	37	26	7	19	4	6	11	5z		z Tuberculosis of the kidney w?	15 days	2 yrs. 10½ mos.	1½ yrs.
131-40	79	68	10	53	20	23	13	7z		z Intra-abdominal hemorrhage z Pneumonia u? v?	2½ mos.	1¼ yrs.	7¼ mos.
41-50	120	100	29	70	32	22	31	15u v w z z z		u? v? w z Sarcoma z Nephritis v Apoplexy z?	10 days	3¼ yrs.	10¼ mos.
51-60	158	130	53	77	32	38	29	31r s t u v w z z z		r Cancer of the stomach s Pneumonia t Apoplexy u? v? w? z? v Pneumonia z Killed	4 days	3 yrs. 5 mos.	9
61-70	77	63	42	22	14	12	19	18r s t u v w z z z		r Gallbladder disease s Cancer of the liver t Cancer of the rectum u Cancer of the pancreas v Cancer w Abdominal cancer z Abscess of lung z? z?	9 days	1 yr. 2 mos.	5½ mos.
71-80	15	13	10	3	13	2	2	5y z		y? z Apoplexy	4 mos.	8 mos.	6 mos..
Total ...	500	390	152	247	106	105	105	81 31 50 cardiac	136		1 mo. 9 days	2 yrs. 2 mos.	9 mos.

B  
UNCOMPLICATED AURICULAR FIBRILLATION

Decade	Total	Patients heard from up to present time	Males	Females	Im- proved	Worse	Un- changed	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
11-20	4	2	0	1	1	1	0	0					
21-30	27	22	13	9	3	5	3	11z y z		z Tuberculosis y Pneumonia z Influenza	6 days	2 yrs. 4½ mos.	9 mos.
31-40	57	39	18	21	5	9	6	19y z		y Pneumonia	13 days	2 yrs. 4½ mos.	11½ mos.
41-50	101	82	34	48	23	20	11	28y z		y ? z Apoplexy	5 days	3 yrs. 3½ mos.	11 mos.
51-60	118	89	39	50	22	13	13	29x y z		z Cerebral hemorrhage y Pneumonia z Cholangitis	3 days	3 yrs.	13 mos.
61-70	50	39	26	13	3	13	2	21w z y z		w Cancer of the tongue z Pneumonia y Diabetes z Peritonitis	14 days	2 yrs. 5 mos.	13 mos.
71-80	104	9	7	2	0	0	3	6y z		y Cancer of the cardia z Cancer of the stomach	4 days	1 yr.	4 mos.
Total ...	367	282	137	144	57	73	28	114 16 98 cardiac	36.9		7¼ days	2 yrs. 5 mos.	10 mos.

B  
UNCOMPLICATED SINUS RHYTHM. CONTROL SERIES

Decade	Patients heard from up to present time		Males	Females	Im- proved	Worse	Un- changed	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
	Total	4	3	1	2	1	2	0			Shortest time	Longest time	Average time
11-20	4	3	1	2	1	2	0	0					
21-30	27	20	4	16	4	5	9	2			15 days	2 yrs.	1 yr. 5½ mos.
31-40	57	47	5	42	15	17	8	7 <sub>v</sub> 1 <sub>w</sub> 2 <sub>x</sub> y z		r ? w Intra-abdominal hemorrhage x Pneumonia y Pneumonia z ?	3½ mos.	1 yr. 3 mos.	9½ mos.
41-50	101	78	20	58	28	14	24	12 <sub>v</sub> w x y z		v ? w ? x Sarcoma y Nephritis z Apoplexy	10 days	2 yrs.	7 mos.
51-60	118	98	38	60	24	27	24	23 <sub>v</sub> w x y z		w Cancer of the stomach x Pneumonia y Apoplexy z ?	4 days	1 yr. 3 mos.	6½ mos.
61-70	50	43	29	14	7	11	10	15 <sub>v</sub> t u v w x y z		s Gallbladder disease t Cancer of the rectum u Cancer of the liver v Cancer of the pancreas w Cancer x Abdominal cancer y Lung abscess z ?	9 days	1 yr. 2 mos.	5½ mos.
71-80	10	9	7	2	1	3	1	4 <sub>y</sub> z		y ? z Apoplexy	4 mos.	8 mos.	6 mos.
Total ...	367	298	104	194	80	79	76	03 26 28 cardiac	16.2		1 mo. 9 days	1½ yrs.	8½ mos.

B<sub>1</sub>

## AURICULAR FIBRILLATION WITH PREMATURE VENTRICULAR CONTRACTIONS

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
11-20	1	1	0	1	0	0	0	1	.....	.....	.....	.....	3 yrs.
21-30	7	5	4	1	0	1	1	3	.....	.....	2 mos.	2 yrs.	2 yrs.
31-40	17	15	8	7	1	2	5	7	.....	.....	5½ mos.	3½ yrs.	1½ yrs.
41-50	20	14	6	8	4	4	2	4	.....	.....	10 days	1½ yrs.	6½ mos.
51-60	26	23	15	8	3	6	8	6	.....	.....	17 days	1 yr. 3 mos.	6 mos.
61-70	16	9	4	5	0	2	1	6	.....	.....	6 days	1 yr. 3 mos.	9 mos.
71-80	2	2	1	1	0	0	0	2	.....	.....	1 mo.	1 yr. 9 mos.	11 mos.
Total.....	89	69	38	31	8	15	17	29	42.0	.....	1½ mos.	1 yr. 10½ mos.	1½ yrs.



B<sub>1</sub>  
PREMATURE VENTRICULAR CONTRACTIONS—CONTROL SERIES

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
11-20	1	0	0	0	0	0	0	0					
21-30	7	5	1	4	0	3	2	0					
31-40	17	14	4	10	2	5	5	2x	....	x Cancer	.....	.....	28 days
41-50	20	17	9	8	2	7	3	5x y	....	x Influenza y Peritonitis	1½ mos. .....	2 yrs. 10½ mos.	1 yr. 8 mos.
51-60	26	19	9	10	3	8	5	3x y	....	x Indeterminate y Cancer	.....	.....	8½ mos.
61-70	16	11	9	2	1	3	2	5	....	.....	5 mos.	2 yrs. 4 mos.	1 yr. 2 mos.
71-80	2	2	2	0	0	2	0	0					
Total...	89	68	34	34	8	28	17	15 5 — 10 cardiac	15.9	.....	3 mos.	2 yrs. 7 mos.	10 mos.

**B<sub>2</sub>**  
**AURICULAR FIBRILLATION WITH ARBORIZATION BLOCK**

Decade.	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
21-30	1	1	1	0	0	0	0	1	.....	.....	.....	.....	11½ mos.
31-40	5	3	3	0	0	0	1	2	.....	.....	3½ mos.	5 mos.	4½ mos.
41-50	7	6	4	2	2	1	0	3	.....	.....	2½ mos.	2 yrs.	1 yr.
51-60	9	8	5	3	0	2	0	6	.....	.....	2 mos.	1 yr. 10 mos.	9 mos.
61-70	9	8	5	3	0	1	3	4	.....	.....	23 days.	1 yr. 4 mos.	8 mos.
71-80	2	2	2	0	0	0	0	2x	.....	x Pneumonia	.....	.....	7 mos.
Total	33	28	20	8	2	4	4	18 1 — 17 cardiac	63.4	.....	2 mos.	1 yr. 5 mos.	9 mos.

**B<sub>2</sub>**  
**ARBORIZATION BLOCK—CONTROL SERIES**

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
21-30	1	1	1	0	0	1	0	0	.....	.....	.....	.....	.....
31-40	5	3	2	1	0	1	0	2x	.....	x Pneumonia	.....	.....	16 days
41-50	7	4	2	2	1	0	1	2x	.....	x?	.....	.....	6 mos.
51-60	9	9	5	4	2	1	1	5x	.....	x?	1 mo.	4 mos.	9½ mos.
61-70	9	8	4	4	0	2	0	3	.....	.....	1½ mos.	1 yr.	6 mos.
71-80	2	2	1	1	1	0	0	1	.....	.....	.....	.....	3 mos.
Total	33	27	15	12	4	5	2	16 3 — 13 cardiac	54.2	.....	1 mo.	7 mos.	5 mos.

B<sub>1</sub>

## AURICULAR FIBRILLATION WITH ARBORIZATION BLOCK AND PREMATURE VENTRICULAR CONTRACTIONS

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
21-30	2	1	1	0	0	0	0	1x	....	x Influenza			
41-50	1	1	0	1	0	0	0	1	.....				2 mos.
51-60	5	4	3	1	1	0	0	3	.....		2½ mos.	1 yr.	8½ mos.
61-70	2	2	1	1	0	0	0	2	.....		1½ mos.	7 mos.	4 mos.
71-80	1	1	1	0	0	0	0	1	.....				1 yr.
Total	11	9	6	3	1	0	0	8 1 7 cardiac	87.5		2 mos.	1 yr.	6 mos.

B<sub>2</sub>

## ARBORIZATION BLOCK WITH PREMATURE VENTRICULAR CONTRACTIONS—CONTROL SERIES

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
21-30	2	1	1	0	0	0	0	1	.....				2½ mos.
41-50	1	1	1	0	0	0	0	1	.....				5 mos.
51-60	5	4	4	0	0	0	0	4	.....				3 mos.
61-70	2	2	2	0	0	1	0	1	.....				10 mos.
71-80	1	1	0	1	0	0	0	1x	....	x Cancer			
Total	11	9	8	1	0	1	0	8 1 7 cardiac	87.5				5 mos.

## C

## AURICULAR FIBRILLATION IN MITRAL INSUFFICIENCY

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
11-20	2	1	0	1	0	0	1	0					
21-30	12	7	5	2	0	3	0	4	.....		2 mos.	2 yrs.	1 yr. 2 mos.
31-40	18	13	11	2	1	2	3	7	.....		1 mo.	1 yr. 10 mos.	7 mo.
41-50	22	17	12	5	3	4	1	9	.....		10 days	2 yrs. 7 mos.	1 yr. 3 mos.
51-60	11	8	5	3	2	2	1	3	.....		1 mo.	1 yr. 1 mo.	8 mos.
61-70	6	5	3	2	0	1	1	3	.....		14 days	1 yr. 1 mo.	7 mos.
71-80	1	1	1	0	0	0	0	1	.....				1 yr. 2 mos.
Total.....	72	52	37	15	6	12	7	27	51.9	.....	1 mo.	1 yr. 8 mos.	11 mos.

## C

## MITRAL INSUFFICIENCY—CONTROL SERIES

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
11-20	2	1	1	0	0	1	0	0					
21-30	12	10	4	6	1	4	5	0					
31-40	18	13	3	10	2	6	2	3x	.....	xPneumonia	9 mos.	1 yr.	11 mos.
41-50	22	17	11	6	2	3	5	7x y	.....	z? y Nephritis	2 mos.	2 yrs.	9 mos.
51-60	11	10	6	4	2	2	2	4	.....		1 mo.	½ yr.	3½ mos.
61-70	6	5	4	1	0	1	1	3	.....		2 mos.	1 yr. 1 mo.	1 yr.
71-80	1	1	1	0	0	0	0	1					
Total. 72	57	30	27	7	17	15	18		27.8	.....	3½ mos.	1 yr.	9 mos.
.....							3			.....		1½ mos.	
.....							15 cardiac						

C<sub>1</sub>

## AURICULAR FIBRILLATION WITH MITRAL STENOSIS

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
21-30	4	3	1	2	0	0	1	2	.....	.....	1 mo.	2 yrs. 4 mos.	9 mos.
31-40	10	5	2	3	0	2	1	2	.....	.....	9 mos.	10½ mos.	10 mos.
41-50	7	5	1	4	1	1	1	2	.....	.....	5 mos.	10½ mos.	7½ mos.
51-60	5	3	1	2	0	1	1	1	.....	.....			
61-70	1	1	1	0	0	0	0	1	.....	.....			½ mo.
Total.....	27	17	6	11	1	4	4	8	47.1	.....	5 mos.	1 yr. 4 mos.	7 mos.

C<sub>1</sub>

## MITRAL STENOSIS—CONTROL SERIES

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
21-30	4	2	1	1	0	0	1	1	.....	.....	.....	.....	2 yrs. 10 mos.
31-40	10	6	4	2	0	4	0	2x	.....	x?	.....	.....	1 yr. 4 mos.
41-50	7	6	1	5	1	2	1	2x	.....	xPneumonia	.....	.....	4 mos.
51-60	5	5	1	4	1	2	1	1	.....	.....	.....	.....	1½ mos.
61-70	1	1	0	1	0	0	1		.....	.....	.....	.....	
Total	27	20	7	13	2	8	4	6 2	22.2	.....	.....	.....	1 yr. 2 mos.
								4 cardiac					

**C<sub>2</sub>**  
AURICULAR FIBRILLATION WITH DOUBLE MITRAL LESION

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
11-20	3	2	1	1	0	1	0	1	.....	.....	.....	.....	3 yrs. 10½ mos.
21-30	6	5	5	0	1	1	1	2	.....	.....	7 mos.	1 yr.	9 mos.
31-40	14	10	4	6	0	2	2	6	.....	.....	3 mos.	1 yr. 10 mos.	10½ mos.
41-50	9	7	2	5	1	1	2	3	.....	.....	1 mo.	3 yrs. 2 mos.	1 yr. 9 mos.
51-60	6	3	1	2	0	1	0	2x	.....	xCholangitis	.....	.....	3 yrs.
61-70	2	2	1	1	0	0	0	2	.....	.....	7 mos.	9 mos.	7½ mos.
Total	40	29	14	15	2	6	5	16 1	53.4	.....	4½ mos.	1 yr. 8 mos.	1 yr. 10 mos.
15 cardiac													

**C<sub>3</sub>**  
DOUBLE MITRAL LESION—CONTROL SERIES

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
11-20	3	1	1	0	0	0	0	1	.....	.....	.....	.....	2 mos.
21-30	6	5	1	4	1	1	2	1x	.....	xInfluenza	.....	.....	.....
31-40	14	12	1	11	1	3	5	3x	.....	xPneumonia	5 mos.	1 yr.	8 mos.
41-50	9	6	2	4	1	1	0	4	.....	.....	1½ mos.	2 yrs. 7½ mos.	10½ mos.
51-60	6	5	3	2	1	1	0	3x y	.....	x? y?	.....	.....	1 yr. 3 mos.
61-70	2	1	1	0	0	0	0	1	.....	.....	.....	.....	1 yr.
Total	40	30	9	21	4	6	7	13 4	34.6	.....	3 mos.	1 yr. 9½ mos.	11 mos.
9 cardiac													

C<sub>2</sub>

## AURICULAR FIBRILLATION WITH AORTIC INSUFFICIENCY

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
21-30	2	2	2	0	0	0	0	2x	.....	x Influenza	.....	.....	10 mos.
41-50	5	3	1	2	0	3	0	0					
51-60	4	3	3	0	1	0	1	1					9 mos.
61-70	2	2	2	0	0	0	0	2			¼ mo.	¾ mo.	½ mo.
Total	18	10	3	2	1	3	1	5 1 — 4 cardiac	44.4	.....	¼ mo.	¾ mo.	6½ mos.

C<sub>3</sub>

## AORTIC INSUFFICIENCY—CONTROL SERIES

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
21-30	2	1	1	0	0	0	0	1					6 days
41-50	5	5	3	2	1	0	1	3x	.....	x?	1 yr. 1 mo.	1 yr. 8 mos.	1 yr. 5 mos.
51-60	4	2	2	0	0	0	0	2x	.....	x?			1 mo.
61-70	2	2	2	0	0	0	0	2x	.....	x Peritonitis			6 mos.
Total	13	10	8	2	1	0	1	8 3 — 5 cardiac	71.4	.....	1 yr. 1 mo.	1 yr. 8 mos.	6 mos.

# AURICULAR FIBRILLATION IN ELDERLY

Decade	Total	Patients heard from, up to present time	Males	Females	Improved	Worse	Unchanged	Percent of cardiac
21-30	1	1	1	0	0	0	1	1
31-40	11	8	5	3	0	4	1	1
41-50	13	10	9	1	3	3	1	1
51-60	31	25	20	5	5	7	3	24
61-70	13	9	4	5	0	5	1	1
71-80	12	10	10	0	0	0	3	27
Total	81	63	49	14	8	19	16	20

71-80	1	1	0	0
Total...	98	77	48	29
				8
				12
				35 cardiac



D  
CHRONIC MYOCARDITIS—CONTROL SERIES

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from Examination until death		
											Shortest time	Average time	Longest time
21-30	1	0	0	0	0	0	0	0					
31-40	11	8	4	4	0	2	1	5x	.....	x Cancer	6 mos.	2 yrs.	1 yr. 4½ mos.
41-50	13	10	5	5	0	5	2	3	.....		2 mos.	2 yrs. 7½ mos.	1 yr.
51-60	31	26	18	8	4	6	2	14x y	.....	x Cancer y Peritonitis	7 days	1 yr. 8½ mos.	5 mos.
61-70	13	11	7	4	1	3	3	4x	.....	x Cancer	1 mo.	3 mos.	1½ mos.
71-80	12	11	10	1	1	2	2	6x y	.....	x? y Pneumonia	3 mos.	6½ mos.	4½ mos.
Total	81	66	44	22	6	18	10	32 6 26 cardiac	43.3	.....	2½ mos.	1 yr. 5 mos.	8 mos.

D<sub>1</sub>

AURICULAR FIBRILLATION IN MYOCARDIAL DISEASE SECONDARY TO HYPERTENSION  
WITH AND WITHOUT CLINICAL NEPHRITIS

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
21-30	2	1	1	0	1	0	0	0					
31-40	3	3	2	1	0	1	1	1	.....				½ mo.
41-50	15	11	5	6	1	1	2	7	.....		1 mo.	10 mos.	5 mos.
51-60	37	25	16	9	4	6	3	12	.....		½ mo.	2 yrs. 10 mos.	11½ mos.
61-70	40	26	15	11	0	5	4	17x y z	.....	x Cancer of the tongue y Diabetes z Peritonitis	1 mo.	2 yrs. 5 mos.	1 yr.
71-80	1	1	0	1	0	0	0	1	.....				1 yr.
Total	98	67	39	28	6	13	10	38 3 35 cardiac	54.7	.....	25 days	2 yrs.	8 mos.

D<sub>1</sub>  
MYOCARDIAL DISEASE SECONDARY TO HYPERTENSION WITH AND WITHOUT CLINICAL NEPHRITIS—CONTROL SERIES

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
21-30	2	1	0	1	0	0	0	1	....	.....	.....	.....	2 mos.
31-40	3	2	1	1	0	0	0	2x	....	z Intra-abdominal hemorrhage	.....	.....	1½ mos.
41-50	15	12	5	7	2	3	1	6z y	....	z Apoplexy y Apoplexy	1 mo.	2 yrs.	10 mos.
51-60	37	28	17	11	4	4	3	17o w z y z	.... .... .... .... ....	o ? w ? z Apoplexy y ? z Cancer	9 days	1½ yrs.	6½ mos.
61-70	40	33	24	9	2	5	5	21w z y z	.... .... .... ....	w ? z Cancer of the tongue y Cancer of the rectum z Hodgkins disease	9 days	2 yrs. 1 mo.	9 mos.
71-80	1	1	1	0	0	0	1	0	....	.....	.....	.....	.....
Total...	98	77	48	29	8	12	10	47 12 35 cardiac	53.8	.....	½ mo.	1 yr. 10 mos.	6 mos.

**D<sub>3</sub>**  
**ATRICULAR FIBRILLATION IN MYOCARDIAL DISEASE SECONDARY TO EXOPHTHALMIC GOITER**

Decade	Total	Patients heard from up to present time	Males	Fe- males	Im- proved	Worse	Un- changed	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Deaths after thyroid-ectomy	Time interval from examination until death		
												Shortest time	Longest time	Average time
21-30	11	10	4	6	1	2	1	6x	....	z Tuberculosis	0	7 days	2 yrs.	7 mos.
31-40	19	17	2	15	5	2	1	9x y	.... ....	z ? y Pneumonia	3	2 mos.	3½ yrs.	11 mos.
41-50	40	33	9	24	11	7	4	11x	....	z Apoplexy	3	5 days	3 yrs.	7½ mos.
51-60	24	22	10	12	9	4	4	5x	....	z Apoplexy	0	3½ mos.	1 yr.	9 mos.
61-70	3	3	3	0	0	1	0	2x	....	z Cancer of the thyroid	0			
Total..	97	85	28	57	26	16	10	33 6 27 cardiac	34.2	.....	6	1½ mos.	2 yrs.	8½ mos.

D<sub>2</sub>

## MYOCARDIAL DISEASE SECONDARY TO EXOPHTHALMIC GOITER—CONTROL SERIES

Decade	Total		Patients heard from up to present time		Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
													Shortest time	Longest time	Average time
21-30	11	8	2	6	0	4	2	2					½ mo.	5 mos.	3 mos.
31-40	19	16	1	15	8	2	4	2	2			rPneumonia			1 yr. 3 mos.
41-50	40	35	6	29	13	14	8	6	z			y? z Tetany	10 days	1 yr. 10 mos.	2 yrs. 7 mos.
51-60	24	23	7	16	12	7	4	4					½ mo.	10½ mos.	4 mos.
61-70	3	3	1	2	0	0	0	0	3				1 mo.	11 mos.	4 mos.
Total	97	85	17	68	33	27	18	17	3		17.1		½ mo.	1 yr.	11½ mos.
										14 cardiac					

D<sub>3</sub>

## AURICULAR FIBRILLATION IN MYOCARDIAL DISEASE SECONDARY TO THYROTOXIC ADENOMAS

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Deaths after thyroidectomy	Time interval from examination until death		
												Shortest time	Longest time	Average time
31-40	3	2	0	2	1	0	1	0	.....	0	0			
41-50	18	16	4	12	8	4	2	2	.....	0	0	3 days	1 yr. 4 mos.	8 mos.
51-60	30	33	6	27	6	6	10	11	.....	0	0	2½ mos.	2 yrs.	10 mos.
61-70	10	8	3	5	1	2	1	4	.....	0	0	5 mos.	2 yrs. 3 mos.	1 yr. 1½ mo.
71-80	1	1	0	0	0	0	0	1	.....	0	0	.....	.....	4 days
Total.....	71	60	13	47	16	12	14	18	30	.....	0	4 mos.	1 yr. 10 mos.	10 mos.

**D<sub>3</sub>**  
**MYOCARDIAL DISEASE SECONDARY TO THYROTOXIC ADENOMAS—CONTROL SERIES**

Decade	Total	Patients heard from up to present time	Males	Females	Improved	Worse	Unchanged	Deaths	Per cent of cardiac deaths	Deaths other than cardiac	Time interval from examination until death		
											Shortest time	Longest time	Average time
31-40	3	2	0	2	2	0	0	0					
41-50	18	16	0	16	10	2	4	0					
51-60	39	35	4	31	8	9	10	8 <sub>v</sub> <i>w</i> <i>x</i> <i>y</i> <i>z</i>	...	<i>v</i> Indeterminate <i>w</i> Cancer <i>x</i> Pneumonia <i>y</i> Killed <i>z</i> ?	2 yrs. 8 mos.	3 yrs. 7 mos.	3 yrs.
61-70	10	8	3	5	1	2	3	2	...	.....	13 days	9 mos.	4½ mos.
71-80	1	1	0	1	0	0	0	1 <sub>r</sub>	...	<i>x</i> Cancer			
Total.....	71	62	7	55	21	13	17	11 6 5 cardiac	8.9	.....	1 yr. 4 mos.	2 yrs. 2 mos.	1 yr. 8 mos.

Letters were sent to all the patients questioning them relative to their cardiac status, and in event of death, requesting the relatives or friends to forward the date and exact cause of death. A third letter was sent in some instances.

A glance at these statistics at once reveals the increased mortality attending heart disease complicated by auricular fibrillation. In most instances the death rate was doubled and trebled. The arrhythmia per se is, of course, not the determining factor.

#### CONCLUSIONS

The mortality attending auricular fibrillation doubles and in some groups trebles that occurring in similar types of heart disease not complicated by this arrhythmia. It is logical to conclude, therefore, that patients suffering from heart disease in whom auricular fibrillation has not occurred have a greater life expectancy.

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# OBSERVATIONS ON CHANGES IN FORM OF THE INITIAL VENTRICULAR COMPLEX IN ISOLATED DERIVATIONS OF THE HUMAN ELECTRO-CARDIOGRAM\*

F. A. WILLIUS

The literature of recent years has contained numerous contributions dealing with abnormalities of the initial ventricular complex Q R S of the electrocardiogram. Most authors, <sup>1,3,4,7</sup> however, have dealt largely with changes affecting all derivations consisting of abnormalities in complex contour or increase in the complex base width exceeding the recognized normal<sup>2</sup>.

Differences of opinion exist as to the cardiac disorder responsible for these deviations from the normal. Most observers, I believe, recognize myocardial changes affecting the ventricular conduction system, locally or diffusely. Robinson<sup>5</sup> takes issue with the majority and emphasizes the rôle of functional myocardial fatigue. He presents electrocardiograms of a patient in which the aberrant complexes approach normal, yet do not attain normal after digitalis and rest. I have not had the opportunity of observing the abnormal complexes' return to normal when all three derivations have been affected. In a previous article<sup>7</sup> I called attention to the high mortality attending this disorder and emphasized the progression of the disease. The obvious criticism of this article is the paucity of necropsy material and the incomplete histologic data. Careful serial histologic examinations have been in progress for some time and will be reported later.

The fact that these patients rapidly show myocardial disintegration and die seems to me to indicate structural changes, in the majority of instances at least, even in the absence of conclusive pathologic data.

The frequency of abnormalities of the Q R S complex in isolated derivations of the electrocardiogram prompted this study to determine, if possible, the clinical significance of these findings. Wedd

\* Reprinted from Arch. Int. Med., 1920, xxv, 550-564.



published 30 such cases in 21 of which a definite clinical diagnosis of heart disease was made and in 19 of which myocardial disease was noted. Three cases were diagnosed syphilis and one was diagnosed chronic nephritis without reference to the cardiovascular system. In 5 cases no clinical diagnoses were recorded. In conclusion, Wedd states, "Slight notching or localized thickening of the R complex of the electrocardiogram is frequently encountered in cases of unquestioned myocarditis . . . . While no quantitative value can be assigned to such notching, it is believed, when permanent, to indicate pathologic changes in the myocardium, and when transient to reveal a temporary or potential defect in the conduction system. . . ."

This study comprises 747 cases and covers a period of five and one-half years. The cases were divided into two major groups, cases (550) with Q R S complexes definitely notched and cases (197) with slurring or localized thickening of the ascending or descending limb, or both. Both groups were subdivided according to derivation occurrence. The accompanying electrocardiograms illustrate the abnormalities under discussion (Figs. 232 to 237).

*Notched Q R S complexes.*—Seventy-seven cases (14 per cent) were placed in Derivation 1, 83 (15.1 per cent) in Derivation 2, and the greatest number, 390 (70.9 per cent), in Derivation 3. In more than half (53.1 per cent) of the cases, the electrocardiograms were associated with preponderance of the left ventricle. Table 1 illustrates this occurrence. This relationship at once directs attention to the left ventricle as the possible seat of disturbance at least in the majority of cases.

Etiologic disorders occurring in this group in order of frequency were (1) degenerative processes, (2) infections, (3) local nutritional disturbances, and (4) congenital heart disease. These findings are summarized in Table 2.

There was definite evidence of heart disease in all except 81 cases (14.7 per cent). This group was clearly separated in order to avoid confusion in the final analysis but it is recorded because the electrocardiographic findings were clear cut. The elapse of more time may throw light on this extremely interesting group.

Negativity of the final ventricular T wave occurred in almost half the cases (41.8 per cent) and was most frequently observed in Derivation 3 (66.4 per cent). There was no instance of T wave negativity in Derivation 2, or in Derivations 1 and 3 in combination. This summary is found in Table 3.

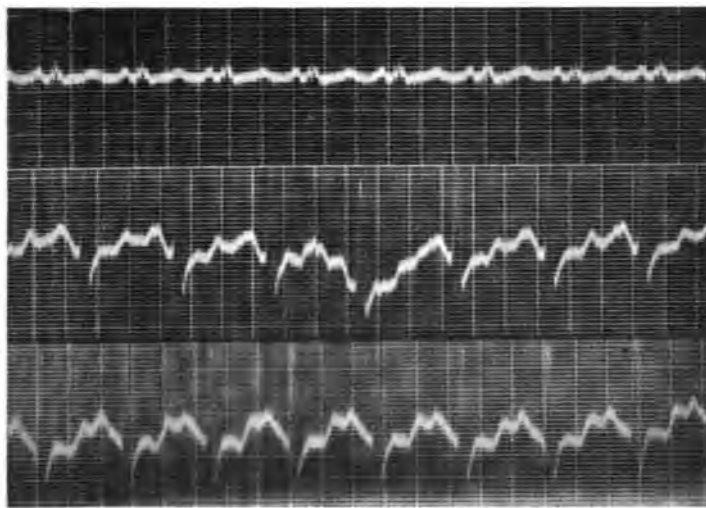


FIG. 232.—(Case 172578). Notched Q R S, Derivation 1.

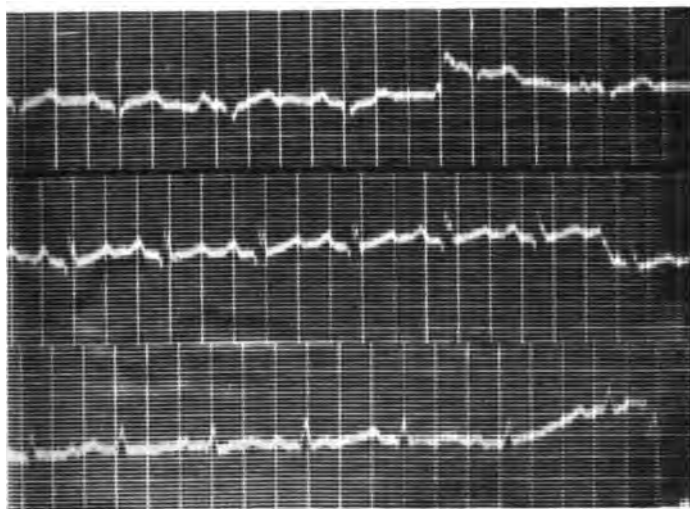


FIG. 233.—(Case 298424). Notched Q R S, Derivation 2.

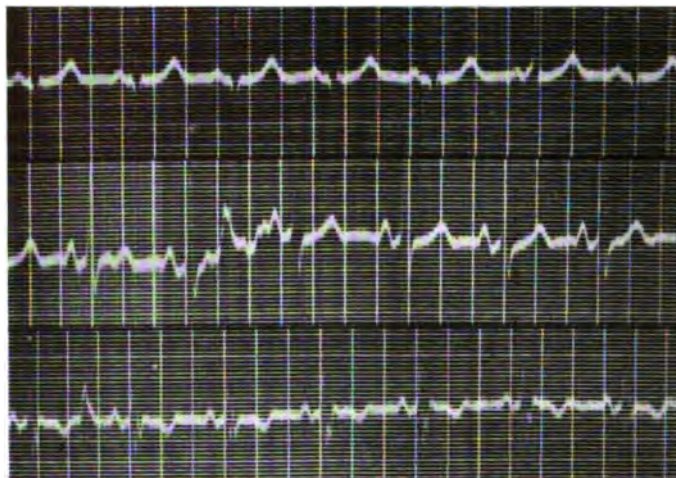


FIG. 234.—(Case 297104). Notched Q R S, Derivation 3.

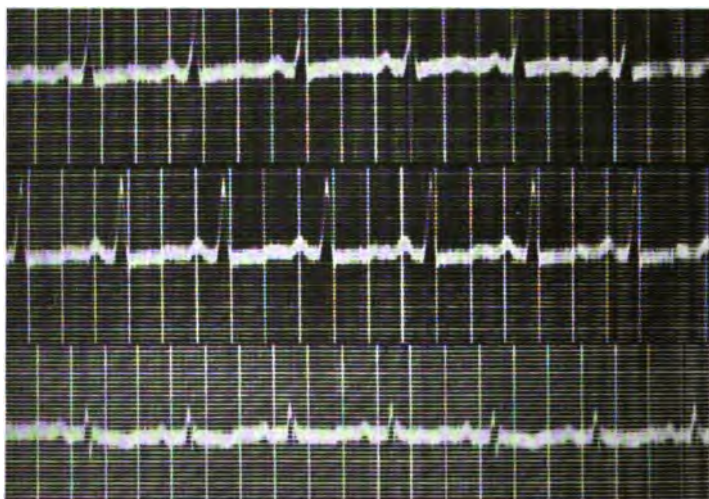


FIG. 235.—(Case 287083). Slurred Q R S, Derivation 1.

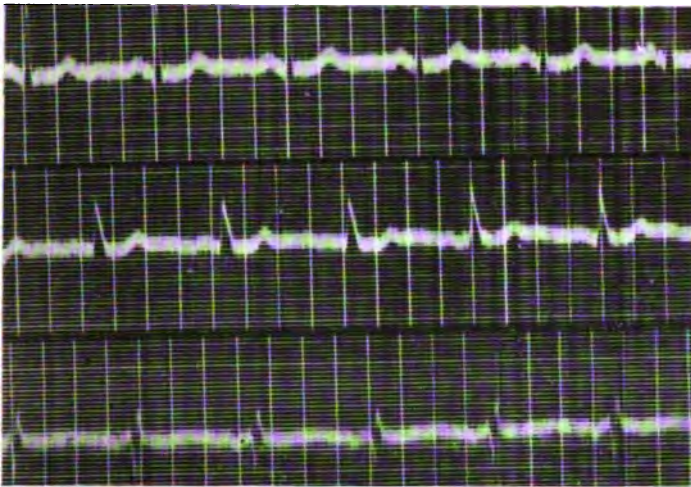


FIG. 236.—(Case 271992). Slurred Q R S, Derivation 2.

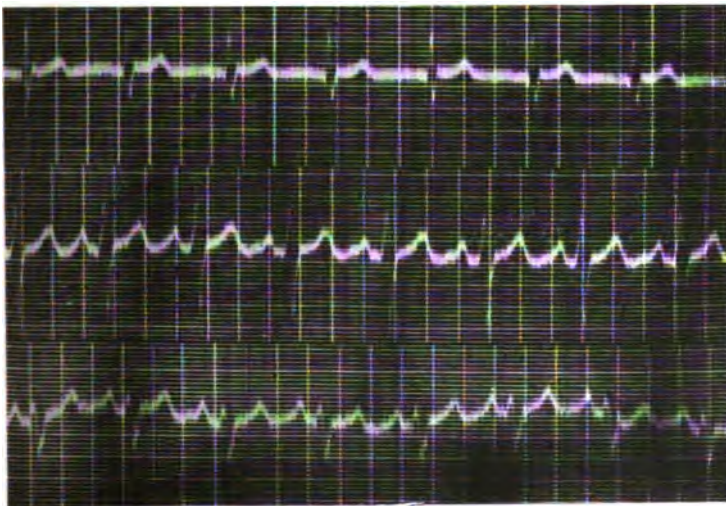


FIG. 237.—(Case 293897). Slurred Q R S, Derivation 3.

Auricular fibrillation occurred in 76 cases (13.8 per cent); this infrequency seems to indicate that these patients as a group are still possessed with relatively efficient myocardiums. Delay in auriculo-ventricular conduction occurred in only 6 cases.

Information has been received concerning 410 patients; 97 (23.7 per cent) of these have died from heart disease. The highest mortality occurred in Derivation 2 (37.0 per cent). A control series corresponding in number, sex, and occurrence by decade and excluding the graver types of heart disease, such as angina pectoris, aneurysm, arborization block, disease of the auriculoventricular bundle, and auricular flutter, revealed a cardiac mortality of 11.8 per cent. This difference in mortality is certainly definite.

Two hundred ninety-seven patients are alive; 94 report their conditions as being worse, 131 as improved, and 72 as unchanged. Thirty-nine report no cardiac complaints. Tables 4 to 8 summarize these findings.

In a previous article I emphasized the significance of the negative T wave in Derivation 1 alone as indicative of myocardial damage. More than one-half (53.6 per cent) of the patients with a negative T wave in this group have died of heart disease. Table 9 summarizes the T wave negativity. This observation demands careful investigation.

*Slurred Q R S complexes.*—This group comprises those Q R S complexes in which localized thickening or slurring of the ascending or descending limb or both occurred. These changes are only slight departures from the normal.

Sixty-seven cases (34 per cent) occurred in Derivation 1, 36 (18.3 per cent) in Derivation 2, and 94 (47.7 per cent) in Derivation 3. Like the cases with notched complexes, the majority (43.6 per cent) were associated with preponderance of the left ventricle (Table 10).

Degenerative processes (34 per cent) and infections (35.4 per cent) occurred equally as causative disorders (Table 11).

The number of cases in which the clinical findings did not corroborate the electrocardiograms was proportionately greater than in the preceding group (42, 21.3 per cent).

About one-third (37.6 per cent) of the cases were associated with negativity of the T wave, again largely affecting Derivation 3 (56.8 per cent). Table 12 illustrates these changes.

Only 16 cases (8.1 per cent) of auricular fibrillation and 6 cases of



delayed auriculoventricular conduction were recorded. Information has been received concerning 150 patients; 36 (24.0 per cent) have died from heart disease. The control series revealed a cardiac mortality of 14.3 per cent (Tables 13 to 17). A definite difference in mortality is again observed. One hundred eleven patients are alive, 32 are in worse condition, 46 are improved, and 33 are unchanged. Eleven patients report no cardiac complaints. Table 18 summarizes T wave mortality.

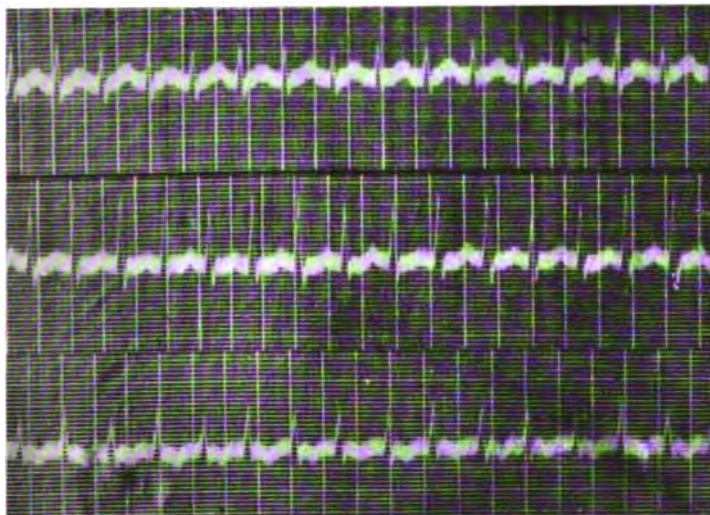
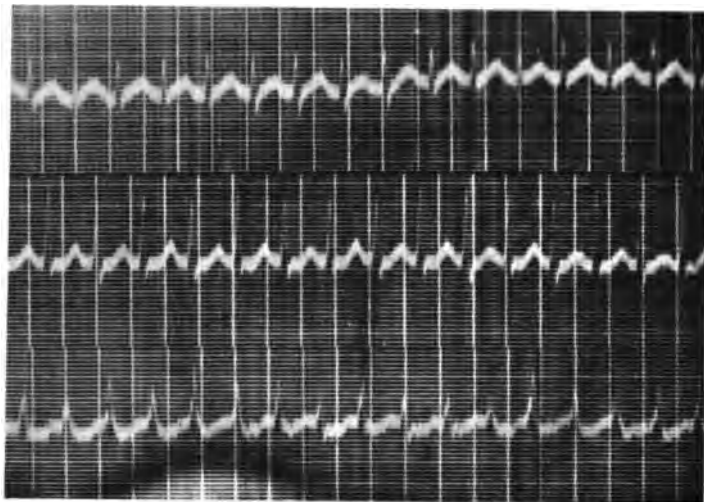


FIG. 238.—(Case 252579). Slurred Q R S, Derivation 3. Negative T wave, Derivation 3. Nodal tachycardia. Feb. 28, 1919.

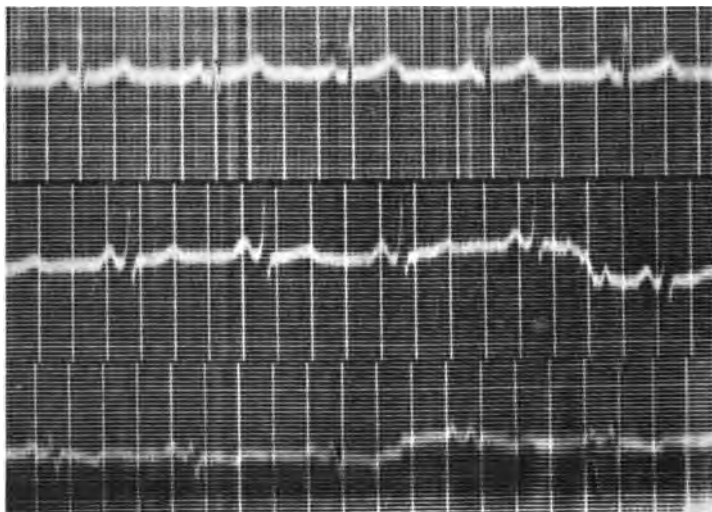
#### DISCUSSION

Notching and slurring of the Q R S complex occurring in isolated derivations of the electrocardiogram suggests a local rather than a diffuse disorder of the ventricles. Whether or not this disorder is structural cannot be definitely stated at present due to the meagerness of necropsy material. The fact that the notched complexes in isolated derivations are identical in contour with those in the cases with involvement of all three derivations makes actual changes in the myocardium a strong possibility.

The slurred complexes are graphically less conclusive, yet they are quite sharply contrasted with the normal. Figures 238, 239, and 240 illustrate progression from slurring to notching and from slight to marked notching.



**FIG. 239.**—(Case 252579). Notched Q R S, Derivation 3, showing progression. Aug. 15, 1919.



**FIG. 240.**—(Case 252579). Notched Q R S, Derivation 3. Sinus rhythm. Aug. 18, 1919, just after tachycardia subsided.

I mentioned previously that a group of cases occurred in which the clinical findings were not sufficient to identify organic heart disease, but in which the electrocardiograms definitely depicted notching or slurring of the Q R S complex (16.5 per cent of total series). I do not believe that organic disease can be definitely excluded in this group. The majority of all the patients (82.5 per cent) had fairly good "compensation" at the time of examination, that is, they were able to be up and about with relative comfort, and no instance of general anasarca was noted. The degree of "decompensation" was recorded as 0 to 2 (on a scale of 1 to 4, minimum to maximum), while in the minority group (17.5 per cent) the grades were 3 to 4. This method of grading myocardial efficiency is of course inaccurate, but it permits comparative study. We are therefore dealing with a group of patients whose myocardiums are quite efficient at the time of examination and it seems possible that muscle changes, especially local disease, can be present before the grosser subjective and objective findings of myocardial disintegration become obvious.

That progression does occur is seen in the electrocardiograms of Case 252579, Figures, 238, 239, and 240 and in the mortality statistics where the percentage in both the notched and slurred complexes nearly doubles those of the control series.

TABLE 1.—VENTRICULAR PREPONDERANCE IN NOTCHED COMPLEXES

Decade	Derivation 1			Derivation 2			Derivation 3		
	Preponderance			Preponderance			Preponderance		
	Left	Right	No	Left	Right	No	Left	Right	No
1-10	3	0	1	0	1	0	2	0	2
11-20	4	0	4	1	0	0	8	3	8
21-30	6	7	10	3	3	0	28	9	25
31-40	4	1	7	4	4	2	35	10	37
41-50	4	4	3	14	3	1	52	10	37
51-60	5	2	6	23	1	2	47	6	23
61-70	2	0	3	14	1	4	25	1	15
71-80	1	0	0	2	0	0	5	0	2
Total.....	29	14	34	61	13	9	202	39	149



TABLE 2.—ETIOLOGIC CONDITIONS IN NOTCHED COMPLEXES

	Total	Degenerative processes			Infections			Nutritional disturbances			Inconclusive clinical cardiac findings
		Hypertension with and without clinical nephritis	Exophthalmic goiter	Adenomas with hyperthyroidism	Endocardial valvular disease	Chronic myocarditis	Syphilis	Arteriosclerosis	Angina pectoris	Patients with arteriosclerosis	Congenital heart disease
Derivation 1	77	6	11	4	39	6	5	3	1	0	3
Derivation 2	83	24	2	3	17	14	3	9	8	3	8
Derivation 3	390	69	84	26	63	42	14	21	12	1	70
Total	550	99	97	33	119	62	22	33	21	4	81
Percentage		18.0	17.6	6.0	21.6	11.3	4.0	6.0		0.07	14.7
		41.6			36.9			6.0		0.07	14.7

TABLE 3.—T WAVE NEGATIVITY IN NOTCHED COMPLEXES

Notched Q R S	Total notched Q R S	T Derivation 1	T Derivation 2	T Derivation 3	T Derivations 1 and 2	T Derivations 2 and 3	T Derivations 1 and 3	T Derivations 1, 2, and 3
Derivation 1	77	1	0	20	1	7	0	2
Derivation 2	83	12	0	18	6	6	0	3
Derivation 3	390	21	0	116	4	12	0	3
Total	550	34	0	154	11	25	0	8
Percentage		14.7	0	66.4	4.7	10.8	0	3.4
232 (41.8)								

TABLE 4.—MORTALITY IN NOTCHED COMPLEXES—DERIVATION 1

Decade	Total	Patients heard from		Deaths		Deaths other than cardiac	Living	Worse	Improved	Unchanged	No cardiac symptoms
		Males	Females								
1-10	4	3	1	2	1	.....	2	0	2	0	0
11-20	8	4	0	4	3	.....	1	1	0	0	0
21-30	23	11	5	6	0	.....	11	4	5	2	0
31-40	12	9	3	6	4x*	x Pneumonia	5	4	1	0	1
				y		y Influenza					
				z		z Abdominal hemorrhage					
41-50	11	8	2	6	4	.....	4	2	0	2	0
51-60	13	10	4	6	4	.....	6	2	3	1	0
61-70	5	4	3	1	2x	x Cancer of the rectum.	2	2	0	0	0
71-80	1	1	1	0	0	.....	1	1	0	0	0
Total.....	77	50	19	31	18	.....	32	16	11	5	1
					14 cardiac						
					28.0 per cent						

\* Each letter refers to a single death other than cardiac.

TABLE 5.—MORTALITY IN NOTCHED COMPLEXES—DERIVATION 2

Decade	Total	Patients heard from		Deaths		Deaths other than cardiac	Living	Worse	Improved	Unchanged	No cardiac symptoms
		Males	Females								
1-10	1	1	1	0	0	.....	1	0	0	1	0
11-20	1	0	0	0	0	.....	0	0	0	0	0
21-30	6	3	1	2	1	.....	2	0	0	2	0
31-40	10	6	1	5	2x	x Pneumonia	4	1	2	1	0
41-50	18	11	6	5	3	.....	8	3	5	0	0
51-60	26	18	12	6	8	.....	10	2	6	2	2
61-70	19	13	11	2	5	.....	8	2	3	3	0
71-80	2	2	2	0	2	.....	0	0	0	0	0
Total.....	83	54	34	20	21	.....	33	8	16	9	2
					20 cardiac						
					37.0 per cent						

TABLE 6.—MORTALITY IN NOTCHED COMPLEXES—DERIVATION 3

Decade	Total	Patients heard from		Deaths		Deaths other than cardiac	Living	Worse	Improved	Unchanged	No cardiac symptoms
		Males	Females								
1-10	4	2	1	1	0	.....	2	0	1	1	1
11-20	19	14	4	10	3	.....	11	1	8	2	5
21-30	62	50	19	31	8	.....	42	10	23	9	7
31-40	82	61	24	37	8 <sub>x</sub> <sub>y</sub>	<sub>x</sub> Diabetes <sub>y</sub> Influenza	53	19	24	10	10
41-50	99	80	29	51	18 <sub>x</sub> <sub>y</sub>	<sub>x</sub> Nephritis <sub>y</sub> ?	62	23	22	17	10
51-60	76	59	37	22	21 <sub>w</sub> <sub>x</sub> <sub>y</sub> <sub>z</sub>	<sub>w</sub> Cancer <sub>x</sub> ? <sub>y</sub> Cancer of the pancreas <sub>z</sub> Pneumonia	38	9	18	11	1
61-70	41	36	25	11	13 <sub>x</sub> <sub>y</sub> <sub>z</sub>	<sub>x</sub> Pneumonia <sub>y</sub> Tuberculosis <sub>z</sub> ?	23	8	7	8	2
71-80	7	4	4	0	3	.....	1	0	1	0	0
Total.....	390	306	143	163	74	.....	232	70	104	58	36
					63 cardiac 20.6 per cent						

TABLE 7.—TOTAL MORTALITY IN NOTCHED COMPLEXES

	Total	Patients heard from	Males	Females	Cardiac deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac symptoms
Derivation 1.....	77	50	19	31	14	28.0	32	16	11	5	1
Derivation 2.....	83	54	34	20	20	37.0	33	8	16	9	2
Derivation 3.....	390	306	143	163	63	20.6	232	70	104	58	36
Total.....	550	410	196	214	97	23.7	297	94	131	72	39

TABLE 8.—CONTROL SERIES

Decade	Total	Patients heard from		Deaths		Deaths other than cardiac	Living	Worse	Improved	Unchanged
		Males	Females							
1-10	9	6	3	3	1	.....	5	2	1	2
11-20	28	17	7	10	3x y	x Thyroidectomy (exophthalmos) y Hyperthyroidism	14	4	6	4
21-30	91	63	23	40	5x y	x Influenza y Hyperthyroidism	58	14	27	17
31-40	104	78	32	46	11w x y s	w Pneumonia x Pneumonia y Pneumonia s Nephritis	67	13	22	32
41-50	128	96	48	48	11v w x y s	v? w Pneumonia x Cancer y Cerebral hemorrhage s Cancer of stomach	85	35	34	16
51-60	115	90	57	33	24s t u v w x y z	s? t Cancer of stomach u? v Pneumonia w Cancer x Peritonitis y? z Pneumonia	66	30	22	14
61-70	65	47	36	11	18u v w x y z	u Cancer of tongue v Cancer of rectum w? x Cancer y Cancer z Apoplexy	29	13	6	10
71-80	10	7	6	1	3x	x Pneumonia	4	1	0	3
Total	550	404	212	192	76		328	112	118	98
					48 cardiac 11.8 per cent					

TABLE 9.—MORTALITY IN T WAVE NEGATIVITY. NOTCHED COMPLEXES

T wave negativity	Total	Patients heard from	Males	Females	Cardiac deaths	Mortality percentage	Living	Worse	Improved	Unchanged	No cardiac complaints
Derivation 1.....	34	28	23	5	15	53.6	11	1	8	2	0
Derivation 2.....	0	0	0	0	0	0	0	0	0	0	0
Derivation 3.....	154	103	33	70	14	13.6	86	31	34	21	10
Derivations 1 and 2.....	11	10	4	6	6	60.0	4	1	3	0	0
Derivations 2 and 3.....	25	17	9	8	4	23.5	10	2	6	2	1
Derivations 1 and 3.....	0	0	0	0	0	0	0	0	0	0	0
Derivations 1, 2, and 3....	8	4	2	2	3	75.0	0	0	0	0	0
Total.....	232	162	71	91	42	25.9	111	35	51	25	11

TABLE 10.—VENTRICULAR PREPONDERANCE IN SLURRED COMPLEXES

Decade	Derivation 1			Derivation 2			Derivation 3		
	Left	Right	No	Left	Right	No	Left	Right	No
1-10	0	1	1	0	0	0	0	0	0
11-20	0	4	1	0	0	0	2	0	0
21-30	2	10	6	2	0	0	3	5	2
31-40	3	6	8	2	2	1	12	5	15
41-50	6	6	4	4	0	6	6	1	6
51-60	5	1	0	9	0	1	16	1	9
61-70	1	1	1	6	0	2	6	1	4
71-80	0	0	0	1	0	0	0	0	0
Total.....	17	29	21	24	2	10	45	13	36

TABLE 11.—ETIOLOGIC CONDITIONS IN SLURRED COMPLEXES

	Total	Degenerative processes			Infections			Nutritional disturbances		Congenital heart disease	Inconclusive clinical cardiac findings
		Hypertension with and without clinical nephritis	Exophthalmic goiter	Adenomas with hyperthyroidism	Endocardial valvular disease	Chronic myocarditis	Syphilis	Arteriosclerosis	Angina pectoris (Patients with arteriosclerosis)		
Derivation 1	67	5	9	2	28	6	2	4	3	1	10
Derivation 2	36	8	3	3	6	5	1	5	4	0	5
Derivation 3	94	22	13	2	10	8	4	7	3	1	27
Total.....	197	35	25	7	44	19	7	16	10	2	42
Percentage.....		17.8	12.7	3.5	22.3	9.5	3.5	8.1	.....	1.0	21.3
		34.0			35.4			8.1		1.0	21.3

TABLE 12.—T WAVE NEGATIVITY IN SLURRED COMPLEXES

Slurred Q R S	Total slurred Q R S	T Derivation 1	T Derivation 2	T Derivation 3	T Derivations 1 and 2	T Derivations 2 and 3	T Derivations 1 and 3	T Derivations 1, 2, and 3
Derivation 1	67	4	0	12	0	6	0	0
Derivation 2.....	36	1	0	10	3	2	0	0
Derivation 3.....	94	3	0	20	0	7	0	4
Total.....	197	8	0	42	3	15	0	4
Percentage.....		10.8	0	56.8	4.0	20.3	0	5.4
		72 (36.5)						

TABLE 13.—MORTALITY IN SLURRED COMPLEXES—DERIVATION 1

Decade	Total	Patients heard from		Deaths		Deaths other than cardiac	Living	Worse	Improved	Unchanged	No cardiac symptoms
		Males	Female								
1-10	2	2	1	1	1	.....	1	1	0	0	0
11-20	5	5	3	2	0	.....	5	1	1	3	1
21-30	18	14	6	8	3x	x Influenza	11	4	5	2	1
31-40	17	14	5	9	5	.....	9	2	3	2	0
41-50	16	12	7	5	9	.....	3	0	3	0	0
51-60	6	6	5	1	3	.....	3	1	2	0	0
61-70	3	2	2	0	0	.....	2	1	0	1	0
Total.....	67	55	29	26	21 20 cardiac 38.3 per cent	.....	34	10	14	8	2

TABLE 14.—MORTALITY IN SLURRED COMPLEXES—DERIVATION 2

Decade	Total	Patients heard from		Deaths		Deaths other than cardiac	Living	Worse	Improved	Unchanged	No cardiac symptoms
		Males	Females								
21-30	2	2	0	2	0	.....	2	1	0	1	0
31-40	5	5	1	4	1	.....	4	0	1	3	1
41-50	10	8	4	4	1	.....	7	4	1	2	1
51-60	10	8	6	2	3x	x Postoperative peritonitis	5	0	2	3	0
61-70	8	5	4	1	2	.....	3	2	0	1	0
71-80	1	0	0	0	0	.....	0	0	0	0	0
Total.....	36	28	15	13	7 6 cardiac 21.4 per cent	.....	21	7	4	10	2

TABLE 15.—MORTALITY IN SLURRED COMPLEXES—DERIVATION 3

Decade	Total	Patients heard from			Deaths	Deaths other than cardiac	Living	Worse	Improved	Unchanged	No cardiac symptoms
		Males	Females								
11-20	2	1	1	0	0	.....	1	0	0	1	0
21-30	10	9	3	6	0	.....	9	5	3	1	0
31-40	32	24	11	13	4x	x Influenza	20	3	13	4	4
41-50	13	8	3	5	1	.....	7	2	3	2	2
51-60	26	17	11	6	5	.....	12	4	4	4	0
61-70	11	8	6	2	1	.....	7	1	3	3	1
Total.....	94	67	35	32	11 10 cardiac 14.9 per cent	.....	56	15	26	15	7

TABLE 16.—TOTAL MORTALITY IN SLURRED COMPLEXES

	Total	Patients heard from	Males	Females	Cardiac deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac symptoms
Derivation 1....	67	55	29	26	20	36.4	34	10	16	8	2
Derivation 2....	36	28	15	13	6	21.4	21	7	4	10	2
Derivation 3....	94	67	35	32	10	14.9	56	15	26	15	7
Total.....	197	150	79	71	36	24.0	111	32	46	33	11



TABLE 17.—CONTROL SERIES

Decade	Total	Patients heard from		Deaths		Deaths other than cardiac	Living	Worse	Improved	Unchanged
		Males	Females							
1-10	2	2	1	1	0	.....	2	0	2	0
11-20	7	6	4	2	1	.....	5	3	0	2
21-30	30	26	10	16	5 <sub>x</sub> y z	x Exophthalmic goiter, (thyroidectomy) y Pneumonia z Exophthalmic goiter (hyperthyroidism)	21	9	3	9
31-40	54	44	14	30	7 <sub>w</sub> x y z	w Pneumonia x? y Postoperative peritonitis z bronchopneumonia	37	16	14	7
41-50	39	27	12	15	6 <sub>x</sub>	x Apoplexy	21	7	8	6
51-60	42	30	19	11	12 <sub>x</sub> y z	x? y Peritonitis z Cancer	18	5	8	5
61-70	14	12	10	2	4 <sub>x</sub> y z	x Cancer y? z Cancer	8	5	1	2
71-80	1	0	0	0	0	.....	0	0	0	0
Total...	197	147	70	77	35 21 cardiac 14.3 per cent	.....	112	45	36	13

TABLE 18.—MORTALITY IN T WAVE NEGATIVITY—SLURRED COMPLEXES

T wave negativity	Total	Patients heard from	Males	Females	Cardiac deaths	Mortality percentage	Living	Worse	Improved	Unchanged	No cardiac complaints
Derivation 1....	8	6	5	1	3	60.0	3	2	1	0	0
Derivation 2....	0	0	0	0	0	0	0	0	0	0	0
Derivation 3....	42	32	10	22	5	15.6	27	4	17	6	3
Derivation 1 and 2.....	3	3	2	1	2	66.6	1	1	0	0	0
Derivation 2 and 3.....	15	15	6	9	4	26.6	11	3	4	4	1
Derivation 1 and 3.....	0	0	0	0	0	0	0	0	0	0	0
Derivation 1, 2, and 3.....	4	4	4	0	3	75.0	1	1	0	0	0
Total.....	72	60	27	33	17	28.3	43	11	22	10	4

## CONCLUSIONS

1. Notching and slurring of the Q R S complex in isolated derivations of the electrocardiogram must be considered as graphic entities.
2. These changes probably indicate local disorders of the ventricular myocardium affecting the conduction system.
3. Etiologic disorders occurring in order of frequency were (1) degenerative processes, (2) infection, (3) local nutritional disturbances, and (4) congenital heart disease.
4. The cardiac mortality in both the notched and slurred complexes practically doubled that of the control series.

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## **BLOOD**



## STUDIES ON ORGAN TRANSPLANTATION\*

### TRANSPLANTATION OF THE SPLEEN WITH INTACT BLOOD SUPPLY

K. KAWAMURA

During the last fifteen years organ transplantation has been studied extensively with especial reference to practical therapeutics and the biologic possibility of regeneration of transplanted tissues.

Many experiments have been reported on the ductless glands, and it has been affirmed that in these experiments the healing of the grafts depends largely on the site of the transplantation, and on the size of the transplant. As to the location of the graft, the opinions of authors differ widely. Cristiani, Ribbert, and others believe that the subcutaneous connective tissue is the best soil for the transplantation of the thyroid tissue: Payr preferred the spleen, while Kocher used the bone marrow. With regard to the size of the transplanting piece Cristiani, Ribbert, and Lubarsch claimed that numerous small fragments of thyroid tissue, the size of a wheat grain, are preferable. Payr, Kocher, von Bramann, and others advised the use of large grafts the size of a hazelnut or cherry because the larger portions undergo destruction.

Many instances of transplantation of the thyroid, parathyroid, ovary, and adrenals are found in the literature, and in some the results were favorable, although the percentage of success was small. On the other hand, reports of the transplantation of the spleen are rare, and the results have been unsatisfactory compared with those of the other ductless glands.

In 1916 Manley and Marine published an article on the transplantation of ductless glands. They transplanted six autografts and eighteen homografts of splenic tissue in the subcutaneous tissue of the abdomen, all of which were absorbed in twelve days. In 1917 they published another article on spleen transplantation. This time twelve attempts at homotransplantation and six attempts at autotransplantation were made on fifteen rabbits. The method employed was the same that was formerly used by them, and consisted of transferring small sections of the spleen of about 2 mm. into the subcutaneous fascia of the abdomen. None of their attempts at homotransplantation was successful beyond the usual results persisting for two or three weeks, common to all homografts. They obtained only one successful permanent autotransplantation. The graft was removed at autopsy three hundred and twenty-five days after transplantation and showed all the morphologic characteristics of a fully differentiated and functionally active spleen. The writers stated that considerable difficulty in spleen transplantation may be due to its complex anatomic structure.

\* Reprinted from *Jour. Exper. Med.*, 1919, xxx, 65-74.

The failure of transplantation of pieces of the organ, however, is partly attributable to insufficient blood supply in consequence of which the grafts are absorbed by degrees. Beside, it should be taken into consideration that small pieces, although successfully transplanted, are not always sufficient for the deficient functions. The transplantation of the entire organ by anastomosis of its blood vessels to suitable parts of the circulatory system can yield sufficient nutrition and probably also function.

Lüdke tried to transplant the spleens of dogs into the splenic vessels of a goat and a wether by blood vessel anastomosis. In all three instances there was faulty blood vessel anastomosis. He attributed the failure in the use of the technic to the unfavorable location of the spleen of these animals, and to the fact that the lumen of splenic vessels is too small. Lüdke, therefore, changed his first plan and transplanted pieces of spleen of rabbits or dogs into the abdominal cavity, the stomach wall, or into the spleen of rabbits, dogs, monkeys, goats, or wethers. The transplanted splenic tissue was observed for four weeks, but after two or three months no part of it was visible.

Carrel extirpated the spleens, washed them out with Locke's solution, and replaced them by blood vessel anastomosis in two dogs. One spleen necrosed and completely disappeared, due to the occlusion of the artery. The replantation of another spleen was successful, so that the anatomic condition of the vessels and of the organs was entirely normal about eight months after the operation.

#### EXPERIMENTAL

The entire series of our experiments was performed on dogs. There are usually two trunks of both artery and vein to the spleen from the gastrosplenic vessels. One pair enters the spleen in its lesser (left) end and another almost in the middle. The spleen was divided in two parts, corresponding to the stream district of these large branches, after the mattress sutures had been applied transversely on it. The half of the spleen which is nourished by the larger branches was used for the transplantation. The attached omentum was cut off after ligation. The splenic artery, vein, and nerves were dissected and divided, Crile clamps being used. The caliber of the artery was hardly 1.5 mm. in diameter. The spleen was then removed, and wrapped in a salt sponge. After a few minutes the spleen was replaced into the abdominal cavity, and its vessels were united as before, by end-to-end anastomosis. In one case an attempt was made to transplant the spleen into the neck. After the thyroid had been removed, the peripheral end of the splenic artery was united to the central end of the superior thyroid artery and the peripheral end of the splenic vein to the central end of the external jugular vein. In another case the spleen was transplanted into the renal vessels after nephrectomy. Most of the experiments were performed autoplastically,

but in one instance the spleen from one animal was transplanted to another. The arterial suture was always difficult, due to the small caliber of the vessel. As soon as the clamps were unfastened, the bluish red collapsed spleen became very red, and its volume was increased. The circulation in the spleen was reestablished between one and two hours after its extirpation. The dissected omentum was reunited, and in a few cases the nerves also were sutured. Several days after the operation the condition of the transplanted spleen was ascertained by laparotomy. When the transplantation was successful, the other intact half of the spleen was removed and immersed in a jar filled with 10 per cent formaldehyde solution for microscopic examination, and the animal was observed further.

The protocol of a successful experiment is given below.

*Experiment 1 (Dog 1).—Adult, mongrel bulldog, male; weight 16.9 kg.*

Oct. 5, 1918. The operation was done under intratracheal ether narcosis. The spleen was exposed through a left rectus incision. Two rows of mattress sutures were placed in the middle of the spleen and the organ was divided between them. One half of the spleen, which was nourished with smaller branches of the splenic artery, was left in the abdominal cavity; the other half was used for replantation. After the dissection of the nerves and omentum, the artery and veins were cut so that this half of the spleen could be brought out extraperitoneally, apart from its connection. The spleen was wrapped up in a salt sponge for a few minutes and replanted into its original site by end to end blood vessel sutures. The arterial lumen measured hardly 1.5 mm. in diameter, and suturing was difficult. The venous suture, on the contrary, was easy. The clamp on the vein was first unfastened and then the clamp on the artery. The spleen, which during the operation appeared dark blue, and was contracted, became normal in color, and assumed its original size as soon as the clamps were removed. The circulation through the replanted spleen was reestablished after an interruption of one hour. No suture of the omentum or the nerves was made. After the circulation through the transplanted vessels as well as the spleen was assured, the abdominal wound was closed. The first incision was made at 9:14 a.m.; the last stitch was inserted at 11:20 a.m.

November 27 (fifty-three days after the first operation). An exploratory laparotomy was done. The weight of the animal was 17.7 kg.; there were no marked adhesions; the omentum was normal. The replaced spleen had kept its original size and appeared entirely normal in color and consistency, but its capsule was thickened. The other intact half of the spleen was extirpated.

December 27. The animal fought with another dog and was seriously wounded in the abdominal wall, back, and both hip regions.

Jan. 1, 1919 (88 days after the first operation). The dog died of his wounds.

*Autopsy.*—The wounds that had been made by fighting were found to be infected; there was no infection of the abdominal cavity. The replaced spleen looked very well. No thrombosis could be found in the splenic artery or vein; their lumina were patent throughout. The suture lines on the vessels could be found with difficulty. They were covered with normal epithelium and were smooth.

*Microscopic examination.*—The capsule was quite thick in places as compared with the control specimen. Otherwise the structure of the pulp, the number and the size of the trabeculae, and the Malpighian bodies were perfectly normal (Figs. 241 to 244).



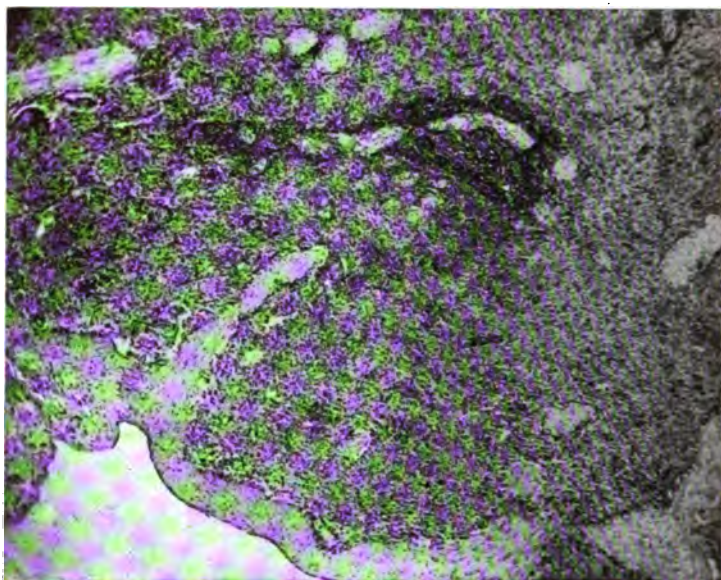


FIG. 241.—Photomicrograph of the intact portion of the spleen of Dog 1. ( $\times 50$ .)

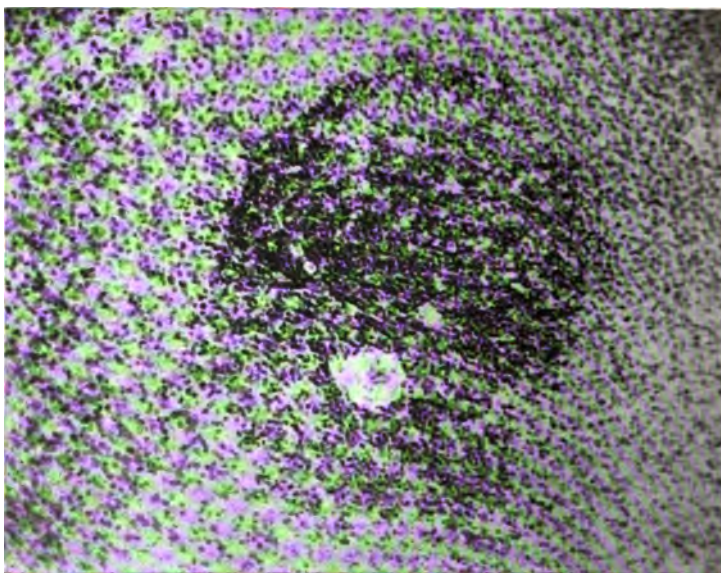


FIG. 242.—Photomicrograph of the specimen shown in Figure 241. ( $\times 125$ .)

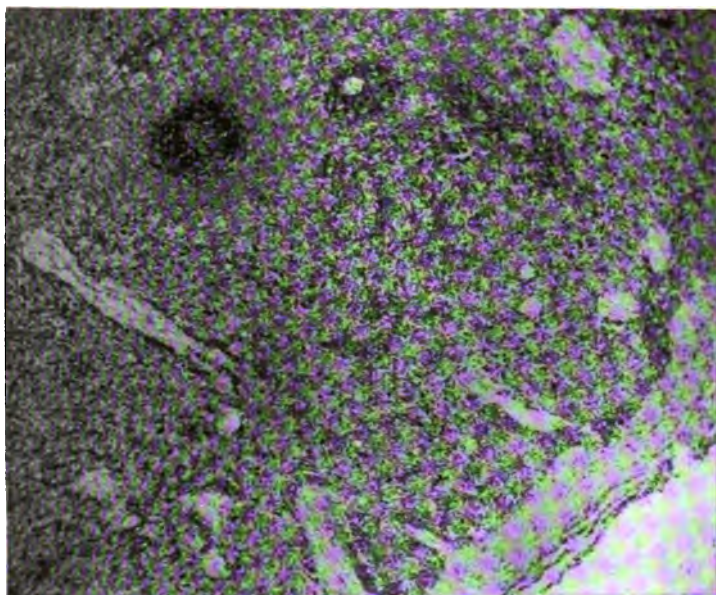


FIG. 243.—Photomicrograph of the transplanted portion of the spleen of Dog. ( $\times 50$ .)

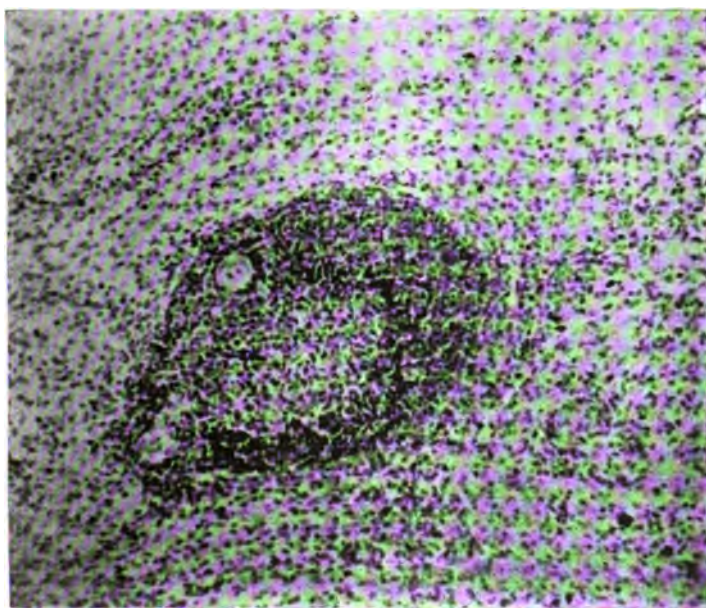


FIG. 244.—Photomicrograph of the specimen shown in Figure 243. ( $\times 125$ .)

TABLE 1.—SUMMARY OF EXPERIMENTS

Experiment No.	Operation	Duration of observation	Results			Remarks
			Condition of blood vessels	Condition of transplanted spleen	Microscopic examination	
1 (Dog 1)	1918 October 5. Replantation of half of spleen. No suture of nerves. November 27. Exploratory laparotomy. Extirpation of other intact half of spleen.	Days 88	Arterial and venous suture in perfect condition. No thrombosis.	Capsule of spleen quite thick. Normal in color and consistency. Surface of section appeared normal.	Shown features of perfectly normal spleen.	December 27. Dog fought with another dog and was severely wounded in several places. January 1, 1919. The wounds proved fatal. October 10. Died. A great deal of bloody fluid filled abdominal cavity.
2 (Dog 2)	October 7. Spleen which was divided in a proportion of one-third and two-thirds by mattress suture replanted, combined with nerve suture.	3	Thrombosis in central part of arterial suture. A small part at venous suture leaked.	Necrotic; softened.		
3 (Dog 3)	October 11. Dividing and replanting of the spleen. Reunion of omentum and nerves.	4	Blood vessels macerated.	Necrotic; softened.		October 15. Died. A great deal of bloody serous fluid in abdominal cavity.
4 (Dog 4)	October 12. After removal of half of the spleen, half of spleen of Dog 9 was transplanted to this dog.	2	Transplanted splenic vein thrombosed.	Necrotic; softened.		October 14. Died. Hemorrhagic serous fluid in abdominal cavity.

5 (Dog 5)	October 16. After removal of left thyroid gland, half of spleen transplanted to neck. Splenic artery united to thyroid artery and splenic vein to external jugular.	7	Both transplanted artery and vein thrombosed.	Necrotic; softened.	Circulation through spleen very good, but volume of spleen became much larger than before transplantation. After operation animal weakened by degrees and died October 23. Died during last operation; very emaciated.
6 (Dog 6)	October 23. Replantation of half of spleen. November 27. At exploratory laparotomy a large cystic tumor was found. January 24, 1919. Extirpation of tumor.	93	Obstruction of artery at united part.	A cystic tumor about size of a child's head grew from replaced spleen. The cyst was filled with a muddy, purulent fluid.	December 23. Animal looked ill. Killed by cutting of femoral artery under general ether narcosis.
7 (Dog 7)	October 28. Replantation of half of spleen and reunion of cut end of omentum and splenic nerves. November 27. Exploratory laparotomy. Excision of a small piece for microscopic examination.	56	Obstruction of transplanted vessels.	Exploratory laparotomy proved that replaced spleen diminished to size of tip of thumb. At autopsy no part of spleen was visible.	Capsule thickened. Peripheral zone of spleen stainable, but central part necrotic. Here and there formations of round holes of several sizes. Connective tissue, leukocytes, infiltration, and fat cells increased.

TABLE I.—*Concluded*

Experiment No.	Operation	Duration of observation	Results			Remarks
			Condition of blood vessels	Condition of transplanted spleen	Microscopic examination	
8 (Dog 8)	1918 November 25. After nephrectomy on left side half of spleen was transplanted to renal vessels.	Days 61	Obstruction of artery at united part.	At second operation it was proved that the transplanted spleen kept its original size, but by incision no fresh blood flowed out. At third operation no part of spleen was visible.	Cells of capsule and subcapsular parts only were stainable.	The animal had been used also for experiments on transplantation of thyroid gland, and duodenectomy. January 31, 1919. Died of intussusception in jejunum.
	December 9. Exploratory laparotomy. From transplanted spleen a small piece was cut off for microscopic examination. January 25, 1919. Exploratory laparotomy.					

Seven attempts at autoplasmic transplantation and one attempt at homoplasmic transplantation of the spleen were made, as shown briefly in Table 1. Five of the seven autoplasmic transplants were replanted to the splenic vessels, one to the neck, and one to the renal vessels. In two of the five replanted cases the dogs died in three and four days after the operation. At necropsy it was found that a great deal of bloody serous fluid filled the abdominal cavity, and that the spleen was necrosed, due to thrombosis. Two cases were examined thirty and thirty-five days after the operation by exploratory laparotomy. One-half of the spleen was found intact in each case, but the other replaced half could not be seen. In one of these two instances there was about 1 liter of pale red, muddy, serous fluid in the abdominal cavity. A round, partly soft, partly hard cystic lump about the size of a child's head lay in the center of the cavity. This lump was surrounded by vast distended blood vessels and muddy gelatinous membrane. Later it was proved at necropsy that the lump was a cyst which had been formed by replanted spleen. The result of one operation (Experiment 1), in which the spleen was replanted in a dog, was highly satisfactory. Eighty-eight days after the operation the spleen, as well as the united blood vessels, was in good condition. The spleen which had been transplanted into the neck was examined seven days after the operation, and it was found that all the tissue had undergone necrosis. The transplantation of the spleen into the renal vessels was troublesome because the field of the operation was too deep and the caliber of the splenic artery was very small. Nevertheless, the immediate result of the operation was successful. As soon as the clamps were removed, the spleen became red and greatly distended. Fourteen days after the operation, when the exploratory laparotomy was made, the spleen retained its original size but the color was pale red, and when it was incised dark blood came out. Forty-seven days later the spleen had completely disappeared. The spleen which was grafted homoplasmically was examined at autopsy two days after the operation. It was soft, dark red, and necrotic. The transplanted splenic vein was thrombosed. Hemorrhagic serous fluid filled the abdominal cavity.

#### DISCUSSION

The results of the experiments immediately after operation were in all cases satisfactory. In spite of the interruption of the circula-



tion for from one to two hours after extirpation, the immediate circulation of blood through the transplanted spleen and blood vessels was favorable, but most of the spleen became necrotic or was entirely absorbed. The cause of this was the obstruction in the transplanted vessels, due to thrombosis. It is probably difficult to obtain good results by using so small a vessel as a branch of the splenic artery. Carrel has noted that such a small vessel cannot be sutured with many chances of success. As has been stated, all Lüdke's experiments failed.

Regardless of these difficulties, our successful case showed that such a highly differentiated, complicated organ as the spleen can be transplanted *en masse*, that it can keep permanently its normal structure, and probably also can functionate normally. In this instance the difference between the central and peripheral parts of the grafts, as Manley and Marine experienced by piecemeal transplantation, was not visible. This is scarcely to be expected because in transplanting by blood vessel sutures the nourishment of the transplant is maintained throughout.

In view of the fact that the spleen can survive even if the nerves are not united, the experiment demonstrated that nerves are not essential for the maintenance of grafts.

The neck, probably also the inguinal furrow, is not a favorable site for the experimental transplantation of the spleen by blood vessel suture, because after the suture of the fascia and skin the more or less distended spleen is compressed, and, consequently, disturbances of the circulation through the graft may occur.

#### SUMMARY

Seven autoplasmic transplantations and one homoplasmic transplantation of the spleens of dogs were made. One autotransplantation was successful, the gland being normal at the end of eighty-eight days.

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## STUDIES ON CHOLESTEROL\*

### VI. THE VALUE OF BLOOD CHOLESTEROL DETERMINATIONS AND THEIR PLACE IN CANCER RESEARCH

GEORGINE LUDEN

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The cholesterol content of the blood has been studied thus far mainly for the purpose of scientific investigation, and its clinical significance has received but little attention. With the exception of Joslin, Rothschild, and perhaps a few others, clinicians seem to be under the impression that cholesterol determinations have little or no practical value.<sup>7,8</sup>

The observations I was able to make between November, 1915, and November, 1918, strongly suggest, however, that the test for cholesterol is capable of giving valuable clinical information, although it should not be looked upon as a specific, diagnostic test, such, for example, as the Wassermann test. It might fitly be compared with the test for albumin in the urine, the clinical value of which is beyond dispute, even though the latter does not enable us to differentiate cystitis and nephritis without other data.

Rothschild has pointed out that in cholelithiasis the absence of a constant hypercholesteremia is due chiefly to the rate of precipitation of the cholesterol in the gallbladder, hence low blood cholesterol values would naturally occur if the surplus cholesterol had been used up in the making of the gallstones, while high blood cholesterol values associated with gallbladder symptoms, in the absence of stones, might merely indicate that the gallstones had not had time to form; that continued hypercholesteremia is well calculated to lead to the formation of gallstones is self-evident.

We are still in the dark concerning the chemical factors which cause the bile-cholesterol to crystallize to gallstones around a nucleus of bacteria and desquamated cells in some cases, while in others no gallstones are formed, although both bacteria and cell detritus are

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present. Rosenow obtained cultures of pathogenic bacteria (streptococci, bacilli Welchi, colon, typhoid bacillus, and others) from the core of ordinary mixed gallstones in 29 of 34 experiments, but found no pathogenic bacteria in 4 pure cholesterol stones. The latter are obviously formed by a more rapid type of precipitation, although we do not know the factors by which this precipitation is brought about. We know, on the other hand, that "typhoid-carriers" may harbor typhoid bacilli in their gallbladders for many years without being afflicted with cholelithiasis. Since the cholesterol content of the bile must be influenced by the cholesterol content of the blood, the study of the latter is eminently fitted to furnish data concerning the cholesterol metabolism resulting in the formation of gallstones.

Apart from the problems connected with cholelithiasis, the cholesterol content of the blood appears to play an important part in growth, both normal and neoplastic. Robertson and Burnett have shown that the rate of tumor-growth in rats can be materially accelerated by intravenous injections of cholesterol, but that, if the structure of the cholesterol molecule is changed (by transformation of "pure" cholesterol into acetyl-cholesterol or cholesterol chlorid, that is, into "changed" cholesterol) the tumors will no longer be affected. The writer<sup>11, 12, 13, 14, 15</sup> has repeatedly called attention to the importance of the blood cholesterol in connection with cell proliferation and was recently<sup>14</sup> able to show that radium treatment increased the amount of changed cholesterol in the blood while reducing the pure cholesterol. The mechanism of this effect of radium is still by no means clear (there seems to be some relation to the lymphocytic and leukocytic reaction), but it was observed that those patients who showed the greatest increase in difference between their pure and changed cholesterol, also appeared to derive the greatest benefit from the treatment. This observation seems specially significant in the light of Robertson's and Burnett's investigations, but it is obvious that massed evidence will be required before we can hope to understand the mechanism involved in the relation between cholesterol metabolism and malignant growth. Further observations by many independent workers are therefore urgently needed. In this connection five points should be emphasized:

1. The nature of the test for cholesterol.
2. The importance of a uniform method for cholesterol determinations.

3. The source of the cholesterol intake.
4. The factors that influence the blood cholesterol.
5. The practical results to be expected in cancer research from the study of cholesterol metabolism.

*Nature of the test for cholesterol.*—Since cholesterol is a definite chemical entity and the test for cholesterol is based on purely chemical reactions, the condition under which determinations are made must control the values that are found in our determinations. In the literature dealing with the cholesterol content of human blood in health and disease, there exists at present a somewhat bewildering lack of uniformity as regards the values given by different writers. In many instances we find the most contradictory statements concerning the blood cholesterol values which accompany pathologic conditions. Such contradictory reports can undoubtedly be explained to a great extent by the varied technic used for the determinations:

1. The many methods used for the extraction of the blood cholesterol.
2. The fact that whole blood was used by some and only blood serum by others.
3. The relative strength or nature of the color standard in colorimetric determinations (it is well known that light shades can be matched more accurately than darker shades of any given color, and that the cholesterol standard and blood cholesterol generally have a slightly different tint).
4. The "setting" of the colorimeter for the standard, because of its influence on the relative depth of color of the standard solution.
5. The temperature at which the determinations were made; a relatively high temperature (35°C., suggested by Autenrieth) tends to produce lower values than does room temperature (20° to 22°C.), a fact to which I have called attention,<sup>11</sup> and which has since been corroborated by Bloor.<sup>5</sup>
6. The time during which the tests are allowed to "ripen."
7. The effect of daylight on the color reaction. Tests left in the dark assume a yellowish-green tone, whereas the same sample will be bluish-green when exposed to the light for the same length of time and at the same temperature. The color of the standard cholesterol always has a tendency to be more bluish (emerald green) than the blood sample and the respective shades can be more accurately matched if the tests correspond in tone.

Another important factor to which I also recently called attention is that there are two distinct types of blood, each with a different rate of color reaction; the rapid and the slow. The rapid type reaches its color maximum ahead of the commercial cholesterol standard and fades more rapidly than the latter. The slow type reacts less quickly but retains its color maximum longer. Unless this peculiarity is duly taken into account, especially when extreme representatives of either type are being tested, the values recorded will not be in accordance with the actual cholesterol content of the sample. Jaundiced patients usually have the very slow type of blood because of the bile derivatives present in the circulation. It has not been possible thus far to determine in what conditions the very rapid type of blood is most frequent; the rapid reaction was found in a good many cases of exophthalmic goiter, but the rapidity of the cholesterol reaction did not seem proportionate to the metabolic rate of the patient. In all our cholesterol determinations special attention has been paid to the rate of reaction of the test, which might introduce an element of error. Bloor has made the same observation and states that "the blood cholesterol behaves differently from the standard cholesterol." A permanent standard would, therefore, undoubtedly offer many advantages, and will be discussed in connection with the need of a standardized, uniform method of procedure.

The blood constituents which are responsible for the different rate of color reaction are eliminated to a greater or lesser extent according to the method used for extraction. They may be looked on in a general sense as changed cholesterol, and are, in part at least, closely related to various bile derivatives.<sup>12</sup>

*Importance of a uniform technic in cholesterol determinations.*—It can not be emphasized too strongly that, unless comparable results are obtained by many observers, it will be impossible to establish the relation of cholesterol metabolism to pathologic conditions. The use of different methods for clinical observations is bound to result in conflicting findings and has undoubtedly been responsible for the conclusion that cholesterol determinations are of little practical value. In biochemic studies the use of various methods offers certain advantages, but for clinical observations a uniform method of procedure would seem a *sine qua non*. If we consider the clinical data supplied by hemoglobinometry, the truth of this statement will straightway be apparent. In hemoglobin determinations the actual color value

of the blood may be influenced by the presence of other blood constituents, but the fact remains that the hemoglobin test has proved a valuable asset to the clinician.

Bloor's methods, which have been used in all our determinations, seem particularly well adapted for clinical work, as they have two advantages: first, the extraction is both simple and complete, and second, the amount of changed cholesterol can easily be determined by means of parallel determinations with the Bloor I and Bloor II methods. Since systematic observations by these methods have already furnished data of clinical interest with regard to the effect of radium on the blood cholesterol,<sup>15</sup> it seems highly desirable that further independent observations should be made along these lines.

A detailed outline of the technic<sup>20</sup> used in our cholesterol determinations will be given in the hope that it may be of use to others working with cholesterol. The outline contains suggestions concerning a number of "pitfalls" to be found in cholesterol determinations, which we learned to recognize while determining the cholesterol content of more than 1500 individual blood samples. (Tables 1 and 2.)

*The source of cholesterol intake.*—Cholesterol ( $C_{27}H_{46}OH$ ) forms a constituent of every mixed diet. Our daily food is therefore a perpetual source of cholesterol intake. To compute a diet that is entirely free from cholesterol but containing the requisite number of calories, as well as the necessary amounts of protein, carbohydrates, fat, and mineral salts, might be a difficult task. Such a diet would probably be very unpalatable and it is doubtful, to say the least, whether it would prove beneficial in the end.<sup>14</sup> Milk, eggs, and butter for instance, which even when we do not use them in pure form are yet to be found associated with most of our food when it is ready for consumption, would have to be eliminated completely. Table 3 shows clearly, however, that certain foodstuffs contain far more cholesterol than others.

Whether the body possesses the power of synthesizing cholesterol from cholesterol-free material is still a matter of dispute. Oatmeal contains no cholesterol, yet when a considerable amount of oatmeal is consumed the blood cholesterol values are markedly increased. This paradoxical phenomenon is still unexplained and, so far as I know, we have no means at our command by which the problem can be solved, though tentative explanations have been suggested in Studies on Cholesterol IV.<sup>14</sup>

Since cholesterol metabolism appears to be a factor in malignant conditions, however, the cholesterol intake in our food seems to deserve more attention than it has hitherto received. We know that in diabetes the metabolism of the carbohydrates is impaired and that

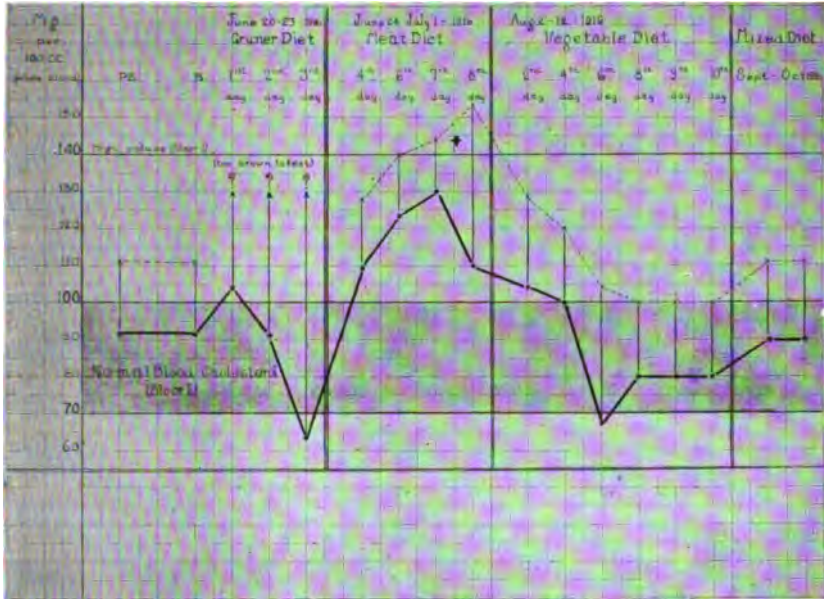


FIG. 245.—PS: The personal cholesterol standard of the writer from January to June, 1916. The tests were made at irregular intervals and showed practically no variations. B: The test taken the day before the experiment was started.

**Gruner's diet:** Milk, water, bread, and lettuce. The Bloor II values could not be determined; the tests were too brown-green because of a great amount of "changed" cholesterol, 's shown by the rapid drop of the Bloor I values (Bloor I solid line, Bloor II dotted line).

**Meat diet:** Meat was used exclusively for every meal, except for a very small piece of bread to "help the meat down" when the latter became very repugnant. + Attack of diarrhea, increasing Bloor II and lowering Bloor I.

**Vegetable diet:** Vegetables and fruit exclusively, tea and coffee as usual. Observe the drop of Bloor I values, and the satisfactory amount of "changed" cholesterol during this period as well as the gradual decrease of the charged cholesterol (vertical line) during the exclusive meat diet before diarrhea intervened, and that no diarrhea occurred on the vegetable diet, but that the blood settled down to a lower level.

**Mixed diet:** Meat twice a day, fruit, vegetables, tea and coffee, no alcohol; the usual type of ordinary mixed diet. Observe that the blood cholesterol returns to its former level.

the pancreas of the diabetic is less efficient than the normal pancreas. Joslin has shown that the treatment of diabetes constitutes one of the triumphs of modern medicine. By eliminating or restricting the use of the foodstuffs that the diabetic cannot "handle," patients

may be kept well and happy. Joslin gives the history of a man (Case 629, pp. 407, 468)<sup>10</sup> whose condition was complicated by tuberculosis and angina pectoris when he came under observation in 1913, but "who still leads an active life at the age of seventy-eight years, and has lately taken up politics." This patient had, however, been kept "under close supervision by a devoted nurse, thoroughly trained in diabetes." If so much can be done for diabetics by safeguarding the weak spot in their metabolism, it seems rational at least to try to lighten the task of cholesterol metabolism for cancer patients by advising them to avoid foods that are rich in cholesterol.\* The cholesterol content of the blood can be increased, even in a healthy person, by the consumption of a great deal of meat (Fig. 245), and that eggs, with their high cholesterol content, are likely to have the same effect is to be expected.

In diabetes chemical analyses supply the means by which we gauge the progress or the exacerbation of the patient's condition, but systematic observations and uniform methods had to be employed over a considerable period before practical results could be obtained; many factors besides the percentage of sugar in the urine had to be taken into consideration in order to reach the therapeutic successes that we observe today.

In carcinoma systematic observations on the cholesterol content of the blood by a uniform method, and in connection with dietetic and therapeutic measures, would not only help to keep us informed, but also very materially further our understanding of the causes of malignant growth.

*Factors that influence the blood cholesterol.*—The amount of changed cholesterol present in the blood is influenced by a number of factors. It is influenced to a marked extent by radium treatment, by the process of digestion (a factor that may, however, be easily eliminated by taking the blood before breakfast), by acute bacterial infections, and apparently by ulceration and hemorrhage. This shows that cholesterol metabolism is influenced directly by any process causing a reaction in the body, that is, by a process that tends to increase the

\* Here again massed evidence will be required. At my suggestion a number of patients have reduced their cholesterol intake, apparently with beneficial results, but sufficient time has not elapsed to warrant definite conclusions. Blood cholesterol determinations and complete blood counts have been made to check up the condition of these patients and the results thus far may be looked on as promising. The details of the observations will be published later. Bulkley has advocated dietetic measures<sup>17</sup> for many years and has recently again emphasized the metabolic origin of cancer.

metabolic rate. In myxedema an inversely proportional relation has been observed between the cholesterol content of the blood and the rate of basal metabolism<sup>14</sup> (Fig. 246). It will also be remembered that the process of spontaneous regression in malignant tumors, whether the tumors be grafted or of autogenous growth, is usually accompanied by ulceration, sloughing or hemorrhage; that radium treatment produces these symptoms as well as a general reaction in many cases; that acute bacterial infections (such as erysipelas, for

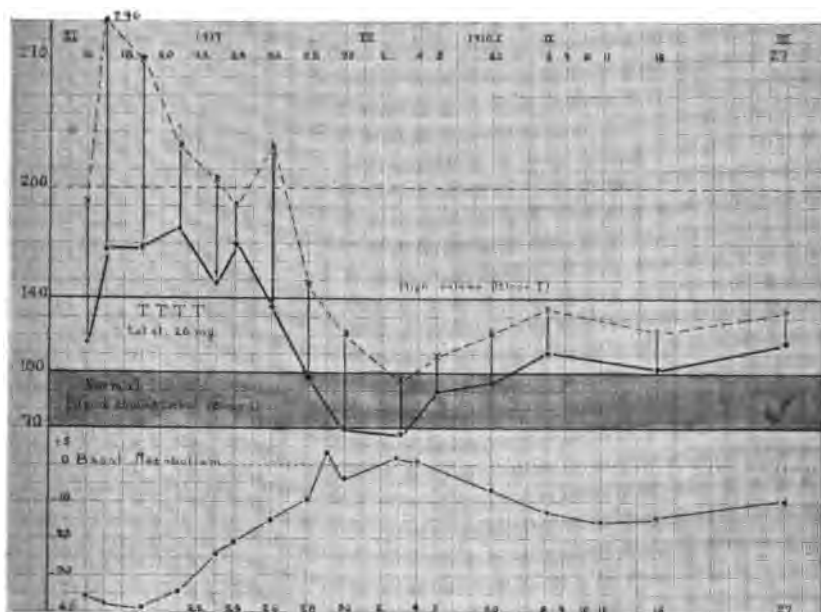


FIG. 246.—The relation between the rate of basal metabolism and the cholesterol content of the blood; observe that it is inversely proportional. The patient, who had a pronounced case of myxedema, went home perfectly well after the administration of the thyroid hormone (Kendall's thyroxin), 5 mg. at each dose.

instance) often exert a curative influence on the growth of tumors, and that the rate of basal metabolism is manifestly increased by all these factors, as shown by the accompanying febrile reaction. Consequently recent bacterial infection, ulceration, sloughing, and hemorrhages will have to be taken into account in the clinical interpretation of our cholesterol values. In the results obtained by Coley's treatment, the reaction plays a prominent part; its effect on the relation between pure and changed cholesterol in the blood would therefore seem well worth investigating.



In this connection I wish to call attention to the significance of Rohdenburg's analysis of 302 cases of spontaneous recession of tumor in man. For the sake of convenience Rohdenburg's Group IA is given in tabular form. This group contains 43 cases (25 of carcinoma, 10 of chorio-epithelioma and 8 of sarcoma) all showing complete recession, carefully controlled. The sequence in which the cases are given in Rohdenburg's article has been observed and the different types of tumors (Tables 4, 5, and 6) have merely been separated. The importance of the fact that these tumors disappeared, and that a patient was well and free from recurrence for a period as long as three and a half years in a case of melanosarcoma and of twenty-two years in a case of carcinoma, can hardly be overestimated. It would seem conclusive evidence that the human body is capable of waging a successful battle against malignant disease, for, in the instances quoted, this battle was fought and won under the most untoward conditions; in some cases the tumors were inoperable and the patients were sent home to die. Their condition would have justified the most pessimistic prognosis; none of them received radium treatment, and the operations that are recorded were for the greater part either "palliative" or "incomplete." Yet tumors, as well as recurrences, disappeared and gave no more trouble.

That the stimulation of the metabolic rate played some part in these recoveries is suggested by the following: Among the cases of sarcoma, bacterial infection intervened in 4 of 8 cases; one case of chorioepithelioma, a "febrile convalescence of six days" is especially mentioned, in another the patient "had a temperature of 41°C. (106°F.) for several days." No febrile reaction is reported in the carcinoma group that showed complete recession, but the reabsorption of the tumors themselves is likely to have stimulated the metabolic rate, to a certain extent, since the reabsorption of body proteins (exudates, hemorrhage) is almost invariably accompanied by a rise of temperature and the latter indicates a rise of the metabolic rate. That a too rapid reabsorption of protein material, by overdriving the organism as a whole, may become fatal to the patient is illustrated by Case 3 in Table 3. In the other instances, however, reabsorption appears to have been less precipitous, and being more gradual, might have insured a continued stimulation of the metabolic processes by which the chemical conditions in the body were effectually altered. Be this as it may, the fact remains that in apparently

hopeless cases the patients became "clinically well" (which after all is the main thing from the patient's point of view) and that they did so under conditions well calculated to increase the rate of their basal metabolism.

Unfortunately we do not possess at present any data obtained by modern methods on the metabolic rate in malignant conditions. I am beginning to collect such data but thus far only two observations have been available; in both instances the metabolism proved to be somewhat below normal. Two observations do not constitute much evidence and a metabolic rate that is only slightly below normal (8 and 11 per cent) may seem insignificant, but it will be conceded that even a slightly subnormal metabolic rate, existing over a prolonged period—half a lifetime, maybe—may as effectually disturb the chemical conditions under which the body cells have to exist, and influence the cells more potently than a marked derangement of metabolism covering a short period. Systematic observations on the rate of basal metabolism in carcinoma before and after radium treatment in connection with the cholesterol content of the blood and the lymphocytic reaction (Murphy's "lymphoid defense") should therefore be looked on as valuable assets in the study of the cancer problem. It is obvious, however, that investigations along these lines cannot be carried out by a single person; here again massed evidence must be obtained in order to furnish conclusive data.

*The practical results to be expected in cancer research from the study of cholesterol metabolism.*—There can be little doubt that the functional inefficiency of one organ may become the primary cause of perverted metabolism; no matter whether that organ has become inefficient after being "damaged" in some way, or whether it was originally inferior through faulty differentiation. The influence of thyroid inefficiency on the metabolic rate in myxedema, and the inadequacy of the pancreas and the chemical derangement it produces need only be recalled.

I have previously suggested<sup>11</sup> that the hereditary transmission of inadequate organs may be a primary factor in the etiology of malignant disease. Since we admit the hereditary transmission of external features (the family nose, the Hapsburg lip) and prove our belief in heredity by the attention devoted to our pedigreed stock, we cannot logically deny that internal organs must also be subject to hereditary transmission. But if internal organs are transmitted thus, it follows

that their inability to do their work properly must also become the cause of faulty metabolism and produce abnormal chemical conditions in the body. Nor is it to be expected that the composition of the blood should be normal under these circumstances, and, since the blood is the main source of food supply for all the body cells, the abnormal chemical composition of the blood is bound to affect the life of the cells, their structure, their development, and their rate of proliferation.

In carcinoma we have not yet been able to recognize the organ that may be chiefly responsible for the type of faulty metabolism that can incite the cells to lawless proliferation. In diabetes, however, we know one organ at least that is unequal to its task, the pancreas. Numerous microscopic studies have failed to reveal any striking histologic changes in the pancreas of the diabetic; the gland seems to be merely functionally inefficient. Moreover, we admit that diabetes "has a tendency to run in families" (Joslin) and thereby indorse the fact of the hereditary transmission of the inadequate gland. By systematic observation on the chemical features that characterize the disease and which are, for the greater part at least, due to pancreatic inefficiency, we are now able to prolong the life or add to the comfort of diabetics to the extent described by Joslin. Had the same amount of energy that has been devoted to the study of chemical and metabolic details in diabetes been similarly employed in cancer research, the verdict "that 90 per cent of those in whom carcinoma develops succumb to the disease"<sup>6</sup> might never have been pronounced. Neither should it be forgotten that the chemical abnormalities observed in the blood of diabetics, high alkalinity, increased sugar content, and hypercholesteremia, are also found in carcinoma.<sup>15</sup> Moreover, cancer very frequently develops in diabetics (Robin, Joslin), whereas it is said that cancer patients rarely acquire diabetes. Possibly the latter statement might have been modified if our chemical data had been collected with equal care in both diseases.

It would be obviously unwarranted, as well as foolish, to ascribe a common origin to conditions that differ so much in their manifestations as do diabetes and carcinoma; but a fundamental similarity may nevertheless exist between them, namely, the functional inefficiency of individual organs; the dissimilarity of the organs that were primarily responsible would naturally determine the course of the diseases in either case.

The results obtained in the treatment of diabetes are sufficiently

striking, however, to stimulate our efforts to discover the source of those metabolic disturbances that promote lawless cell proliferation. Blood cholesterol determinations, made systematically in conjunction with observations on the rate of basal metabolism and on other chemical constituents of the blood and urine, as well as the cytology of the blood, might reasonably be expected to further our knowledge in this direction. The study of the lipoid metabolism is as yet in its infancy, but its relation to carcinoma seems unquestionable in the light of Robertson's and Burnett's investigations.

It is for this reason that determinations of the blood cholesterol, one of the chief blood lipoids, should have a place in cancer research.

#### TECHNIC

1. *Extraction.*—The ether-alcohol extract of the blood is prepared according to Bloor's direction, namely, 3 c.c. of blood taken from the cubital vein by means of a graduated syringe, are squirted directly into 75 c.c. of the ether-alcohol mixture ( 3 parts 95 per cent alcohol to 1 part ether per 100 c.c.), well shaken to insure a fine division of the blood, just brought to the boil on the water-bath, the bottle being shaken slightly all the time to prevent overheating, cooled under the tap for about five minutes, and then filtered. The bottles are filled up to 100 c.c. if the tests can be made immediately, otherwise they are merely corked, sealed with paraffin, and kept in a cool place to be filled up before the tests are to be made. This routine was adopted for the sake of greater accuracy, as the ether is bound to evaporate somewhat and thereby increase the concentration of the extract. Observations have shown that most extracts will remain unchanged for from one to six months; others, however, show variations in the relation of the changed and the pure cholesterol, due presumably to a disintegration of the cholesterol molecule, so that it is safer to make the tests as soon as possible after the blood has been drawn. We do not use citrate and have not had any trouble through clotting of the blood. Sodium citrate appears to affect the cholesterol values in some types of blood (no explanation can be offered for this observation, but the matter is being investigated); we have, therefore, discarded its use in order to insure similar conditions for all our tests. The extracts are kept in graduated 100 c.c. bottles, care being taken that no increase of concentration has occurred in samples that are to be retested after weeks or months.

For the Bloor I tests, 2 c.c. of sodium ethylate (3 gm. of metallic sodium dissolved in 100 c.c. of absolute alcohol) are added to each 10 c.c. of ether-alcohol extract; for the Bloor II tests, no sodium ethylate is added. We use 30 c.c. of the extract for each determination, so as to have enough material for three tests in each case. The extracts are measured into beakers and evaporated to dryness on a water-bath. As soon as they are dry the samples are taken off the water-bath, to avoid overheating, and left to cool for from fifteen to twenty minutes. The residue in the beakers (a faint yellow layer in the Bloor I, but hardly visible in the Bloor II samples) is then extracted three times with small quantities of dry chloroform. Any trace of water in the chloroform interferes with the subsequent color reaction. We have found it convenient to keep the chloroform in a wide glass bottle into which has been placed a quantity of calcium chlorid; the chloroform is filtered before it is used. Each 10 c.c. of the ether-alcohol extract should provide 6 c.c. of chloroform extract when the three extractions have been added together, a total of 18 c.c. of chloroform extract being obtained when 30 c.c. of ether-alcohol extract is used per sample, as in our determinations.

2. *Color reaction.*—To 6 c.c.\* of the chloroform extract are added 2 c.c. of acetic acid anhydrid and 0.2 c.c. of water-free concentrated sulphuric acid. We use ordinary test tubes, and shake the chloroform and reagents well to insure thorough mixing. We have found that the use of 0.2 c.c. instead of 0.1 c.c. as generally recommended, has the advantage of producing a tone of green that can be matched more readily, but does not influence the cholesterol values (the same amounts of the reagents are, of course, added to the cholesterol standard). Since the color reaction is due to oxidation, it seemed possible that the use of more sulphuric acid might increase the amount of changed cholesterol. This, however, is not the case. On the contrary, in a series of some 20 samples tested both with 0.1 and with 0.2 c.c. of sulfuric the amount of changed cholesterol was slightly higher with only 0.1 c.c. in some cases, though it was not altered in the majority of them. This observation is important, because in a series of determinations of the blood cholesterol in carcinoma of the cervix before radium treatment we had found, much to our surprise, that the

\* Six cubic centimeter tests were originally recommended by Bloor. We are using them as this greater volume is more satisfactory in the large Duboscq colorimeter, the plungers do not get out of their depth in samples containing little cholesterol.

number of patients whose blood gave equal values with the Bloor I and II tests was very small, whereas in the series previously reported,<sup>15</sup> including diverse localization of the disease, the percentage of equal values had been high (56 per cent). Since the use of more sulfuric acid lessens the changed cholesterol but certainly does not increase it, the behavior of the blood in carcinoma of the cervix (namely, the relatively big amounts of changed cholesterol) cannot be due to our technic, but must be due to other factors. As most of the patients suffering from carcinoma of the cervix had a history of severe hemorrhage or of ulceration, these two factors would seem to influence the amount of changed cholesterol in the blood.

3. *Technic used in the test.*—After the reagents are added, the test tubes are left exposed to the light at room temperature (20° to 23°C.) for five minutes; this enables us to watch the rapidity of the color reaction as compared with the standard cholesterol and helps us to decide whether the blood sample is of the slow or of the rapid type. It also causes the tests to assume a tint of green that is more easily matched. After five minutes the tests are poured from the test tube, into the colorimeter containers. Colorimetric readings are made at a few minutes' interval from five to fifteen minutes after the reagents are added. The reading which persists at least four times is recorded as the maximum value. The cholesterol standard begins to fade in about twenty minutes<sup>12</sup> and for this reason we never use a standard that is more than fifteen minutes old. The reagents should be added to the standard and to the sample as nearly simultaneously as possible, and a fresh standard should be used for each sample. Table 1 has been found a great convenience in our determinations, as it gives the cholesterol values in milligrams per 100 c.c. directly from the colorimetric reading.

4. *Permanent standard solution "NBM."*—Lately we have made observations with a permanent standard, the color value of which corresponds to the cholesterol standard given in Table 1. This standard solution and the pure Naphthol Green B Solution recommended by Gorham and Myers can only be called "permanent" in a restricted sense; the solution itself will keep unchanged in the bottle, even when exposed to light, but the portion of it used in the colorimeter and thereby exposed to fumes of the reagents, changes its tone and decreases in color value. This is especially true if the closed Kober colorimeter is employed. Those who work with the latter in-

strument will have observed that a strong odor of acetic anhydrid is retained in the instrument for some time after the tests have been taken out. As our containers and plungers were cleaned with special care and washed, first in a strong solution of sodium bicarbonate, then repeatedly with distilled water to remove all trace of acid, actual contact with acid cannot be responsible for this deterioration of the Naphthol Green B, or of the NBM standard solution, which will, of course, result in inaccurate readings if the standard is looked on as truly permanent. We have found, however, that satisfactory and reliable results are obtained if the standard solution is renewed after each two or three samples have been tested. As in all our observations parallel determinations are made with two colorimeters, a standard cholesterol solution being used in one of them, while the reliability of the aqueous standards was being checked up, it was, of course, relatively easy to discover when the aqueous solution began to "go off." For those who only use one colorimeter, we would recommend changing the aqueous standard fairly often to insure the greatest accuracy. Even so the use of the aqueous standard will be found to be both convenient and economical. The NBM standard solution has a decided advantage in our estimation when compared with the pure Naphthol Green B, inasmuch as the latter is yellow green in tone and is much more difficult to match to the more bluish green of many of the blood samples, especially if the tests are left exposed to the light during the process of ripening as I have recommended.

*Formula of the NBM standard solution.*—NB stock solution; Naphthol Green B, 0.5 gm. to 100 c.c. of distilled water (0.5 per cent solution); M stock solution; methyl blue, 60 mg. to 100 c.c. of distilled water (0.06 per cent solution).\* NBM standard solution: 1 c.c. of NB stock solution and 1 c.c. of M stock solution to 200 c.c. of distilled water. Stock solution NB should be added first to the 200 c.c. of distilled water, well stirred or shaken, after which stock solution M is added; if both stock solutions are mixed before dilution a precipitate is apt to form which can be prevented if the naphthol green is diluted before the methyl blue is added.

\* Our Stock Solutions were made up in December, 1917, and have been found to be unchanged by testing them at intervals of several months against pure cholesterol standards up to the present, January, 1919. They have been exposed to the light all the time.

TABLE 1.—CHART FOR BLOOD CHOLESTEROL DETERMINATIONS

Giving the Cholesterol Value in mg. per 100 c.c. Directly from the Colorimetric Reading

Standard: 0.4 mg. cholesterol to 6 c.c. of chloroform.\* (This concentration harmonizes best in color with the value found in human blood.) The NBM permanent standard is equally satisfactory (for formula see text).

Set at: 10 mm.—Colorimeter: Duboscq and Kober.

Cholesterol values in mg. per 100 c.c. of whole blood																				
Mm.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.
	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.
	1332	666	440	333	267	222	191	167	148	133	121	111	102	95	89	83	78	74	70	67
Mm.	L.N.																			
0.1	1210	636	430	326	261	218	188	164	146	132	120	110	102	95	89	83				
0.2	1110	603	417	318	259	216	186	163	145	131	118	109	101	94	88	82				
0.3	1020	580	410	310	251	212	183	162	144	129	117	108	100	93	88	82	77	73	69	66
	H.N.																			
0.4	950	555	392	304	249	208	180	159	142	128	117	107	99	93	87	81				
0.5	895	533	380	296	241	204	177	157	140	127	116	107	99	93	87	81	76	72	68	65
	high																			
0.6	840	515	370	290	238	202	175	156	138	126	115	106	98	92	86	80				
0.7	785	495	360	284	234	200	173	154	136	125	114	105	98	91	85	80	75			
	except																			
0.8	745	477	352	278	230	198	171	152	136	124	113	104	97	91	85	79				
0.9	705	460	341	272	226	194	169	150	135	123	112	103	96	90	84	79	74	72	67	76
	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.	mg.
Mm.	21.	22.	23.	24.	25.	26.	27.	28.	29.	30.	Values below 63 mg.: rare in human blood but usually found in goat's blood.									
	63	60	58	55	53	51	49	48	46	44										
0.5	61	59	57	54	52	50	48	47	45	43										
	mg.										mg.									
Mm.	40.	45.	50.	60.	70.	80.	These values do not occur in blood but were used in color determinations of "bile derivatives."													
	33	30	27	21	19	17														
	mg.																			

The designation of "normal" (70 to 100 mg. per 100 c.c. of whole blood) is based on the use of the Bloor I method, with the "standard" and setting of the colorimeter indicated above. Values between 100 and 140 mg. usually were found to occur in inflammatory conditions (digestion of course being excluded for every test); we refer to them as "increased."

Values between 140 and 200 mg. are referred to as "high" values with the Bloor I method. Values over 200 mg. were only observed in a few cases (3 cases of myxedema, one carcinoma) they have therefore been called "exceptional" in our determinations.

In carcinoma "high" values are the usual finding, though "increased" and (rarely) normal values have been observed. "Equal values," that is identical with the Bloor I and II methods, were found in 56 per cent of the cases of carcinoma in which radium treatment was to be given.

After radium treatment the Bloor I values were found to drop, whereas the Bloor II values increased, causing the "equal values" to disappear. No "equal values" have been found so far in non-malignant cases.

N.B.—It should be remembered that the cholesterol test is not a diagnostic test; it is merely a "clinical" test, like the test for albumin in the urine.

\* Stock Solution = 200 mg. of cholesterol in 100 c.c. of pure chloroform.

Standard Solution = 10 c.c. of A made up to 150 c.c. with pure chloroform.



TABLE 2.—TESTS MADE WITH NBM PERMANENT STANDARD

1. "Standardizing" of the Duboscq and Kober colorimeter against each other with ordinary cholesterol standard. One side of the colorimeter is used exclusively for the standard and marked S. Double samples of the standard cholesterol are prepared and one of these is used as "unknown," in both the Duboscq and Kober. Standard set at 10 mm., "unknown" reads 10 mm., 3 times by three observers. This shows that both Kober and Duboscq give identical readings.	
2. Duboscq: Cholesterol standard 5 to 10 minutes old, set at 10 mm. NBM used as "unknown." Readings: 10.1 mm. 10 mm. 10 mm. 9.9 mm. 10. mm. 10.1 mm. 10.1 mm. 10 mm. 10 mm. = 133 mg. 132 mg. 135 mg. 133 mg. 132 mg. 133 mg.	
3. Kober: Procedure as above, readings vary within same limits, between three observers..	
4. Kober: NBM standard set at 10 mm. blood sample as "unknown."	
Sample A	Duboscq: Cholesterol standard at 10 mm. blood sample used as "unknown."
Bloor I 20 mm. 20 mm. 19.9 mm. 19.9 mm. .... 19.9 mm. 19.9 mm. 19.9 mm. 20 mm. = 67 mg. 67 mg. 67 mg. 67 mg.	
Bloor II 11.3mm. 11. mm. 11.1mm. 11. mm. .... 11 mm. 11.2 mm. 11. mm. 11. mm. = 117 mg. 121 mg. 120 mg. 121 mg. 121 mg. 118 mg. 121 mg. 121 mg.	
Sample B	
Bloor II 9.2 mm. 8.2 mm. 8.8mm. 8.8mm. .... 8.1 mm. 8.8 mm. 8.7 mm. 8.8 mm. = 145 mg. 152 mg. 152 mg. 152 mg. 164 mg. 152 mg. 154 mg. 152 mg.	
Sample C.	
Bloor I 11.7 mm. 11.7 mm. 11.7 mm. 11.7 mm. .... 12 mm. 11.9 mm. 11.9 mm. 12 mm. = 114 mg. 114 mg. 114 mg. 114 mg. 111 mg. 112 mg. 112 mg. 111 mg.	
Bloor II 9mm. 8.9 mm. 8.8 mm. 8.9 mm. .... 9.1 mm. 8.8 mm. 9.1 mm. 8.7 mm. = 148 mg. 154 mg. 152 mg. 150 mg. 146 mg. 152 mg. 146 mg. 154 mg.	
Sample D: A mixture of all the remnants of Bloor I and Bloor II tests made that morning of which the cholesterol value was naturally beyond guessing. 10 mm. 10.1 mm. 10.2 mm. 10.1 mm. .... 10 mm. 10 mm. 10.1 mm. 10 mm. 133 mg. 132 mg. 131 mg. 132 mg. .... 133 mg. 133 mg. 132 mg. 133mg.	

TABLE 3.—CHOLESTEROL VALUE OF FOOD  
(Mg. Cholesterol per 100 c.c. or 100 gm.)

3 gm. sample	Bloor I	Method	Bloor II
Yolk of egg (raw).....	888		888
Yolk of egg (hard boiled).....	888		888
Butter.....	157		298*
Chicken (roasted breast).....	127		127
Beef (raw).....	53		53
Beef (roast).....	63		63
Beef (smoked, salted, dried).....	60		83**
Fish, black bass.....	83		83
***Mushrooms (plain cooked, agaricus campestris).....	140		102
Mushrooms (stewed in butter, another batch of agaricus campestris).....	70		60
Cream (raw).....	61		61
Milk (raw).....	28		28
Oatmeal (boiled porridge).....	0		0

\* Probably due to some coloring matter, eliminated in Bloor I by sodium ethylate.

\*\* Reddish tone of ether alcohol extract suggests coloring matter, eliminated in Bloor I by sodium ethylate.

\*\*\* Mushrooms contain phytosterol, a substance allied to cholesterol, but give the green reaction with the usual reagents; the lower value with Bloor II is an unusual phenomenon, for which no explanation can be offered, probably due to the phytosterol itself.

TABLE 4.—SARCOMA: 8 CASES

\* Group 1A Complete Recession, Carefully Controlled

Description of first findings		Time elapsed until second findings	
Melanosarcoma, back-axilla	Primary tumor involvement of axilla removed by operation	3½ years	Still free from recurrence
Round-cell sarcoma, chin cervical glands	Chin, operation, recurrence in right and left cervical glands. Left cervical removed	No time given	Spontaneous recession after erysipelas of remaining nodules
Round-cell sarcoma, axilla	Operation, recurrence, incomplete curetting	13 months	No recurrence, remnants of tumor disappeared after erysipelas
"Sarcoma," axilla	Many metastases; pregnancy followed by abortion	No time given	Tumors disappeared; patient died six weeks later
Fibrosarcoma, skull	Secondary deposits, partial removal	No time given	All tumors disappeared
Round-cell sarcoma of the breast	Many metastases in subcutaneous tissues	No time given	All neoplastic deposits disappeared after acute infection of lung (pneumonia?)
Lymphosarcoma behind the ear	Inoperable	No time given	Complete recession after inoculation with erysipelas

One case of melanosarcoma showed regressive changes but "changes did not progress to the degree of clinical manifestation."

\* Rohdenburg, G. L.: Fluctuations in the growth energy of malignant tumors in man, with especial reference to spontaneous recession. *Jour. Cancer Res.*, 1918, iii, 193-225.

TABLE 5.—CHORIOEPITHELIOMA: 10 CASES

\* Group 1A Complete Recession, Carefully Controlled

Description of first findings	Time elapsed until second findings	
Fundus uteri perforated, bladder involvement, part of tumor attached to bladder	16 months	Patient well, no mass palpable (febrile convalescence of 6 days)
Uterine wall perforated, pelvic involvement; incomplete removal	1 year +	At autopsy no recurrence was demonstrable
Invasion of uterine muscle; curettage	1 year	Patient well
Cherry-sized tumor, posterior wall, tumor removed	10 weeks	Curetting, no abnormal histology
	1 year	Patient clinically well
Nodule in vagina removed; recurrence 2 weeks later; suppuration and disappearance	10 months	Patient well
Nodules in vaginal wall and uterus $2\frac{1}{4}$ years after hydatidiform mole had been delivered; nodules removed	10 months	No evidence of recurrence
Chorio-epithelioma curetted; temperature 106 (41°C.) for several days.	29 days	Second curetting, negative
		Subsequently bore two healthy children
Abortion at $7\frac{1}{2}$ months; curettage	1 year	Tumor and metastasis disappeared
Metastases shortly after. Sent home to die (case Hörman)		Subsequently normal pregnancy

In the two remaining cases no malignancy was found after curettement in serial sections of the uterus removed by hysterectomy only a short time afterward; consequently they hardly constitute evidence of regression.

\* Rohdenburg, G. L.: Fluctuations in the growth energy of malignant tumors in man, with especial reference to spontaneous recession. Jour. Cancer Research, 1918, iii, 193-225.

TABLE 6.—CARCINOMA: 25 CASES

\* Group 1A Complete Recession, Carefully Controlled

Location of first findings	Time elapsed until subsequent findings	
<b>Stomach:</b> Advanced, widespread peritoneal metastasis, ascites	2½ years	Autopsy, no local recurrence; metastasis and ascites absorbed
<b>Tonsil-tongue:</b> So extensive as to be inoperable; not treated, mouth wash used; patient sent home to die	18 months	No trace of original tumor
<b>Breast:</b> Amputation 1904; recurrence, 1906, August (x-ray); practically moribund until December, 1906	Dec. 28, 1906	Sudden, "overnight" absorption of entire area; patient died three weeks later
<b>Breast:</b> Amputation; recurrence in scar metastases in liver	Next few years	No treatment, recurrences disappear; patient subsequently "entirely recovered"
<b>Uterus:</b> 1 fundus, 2 cervical, all inoperable; palliative cauterization, curetting	6 to 7 years	All clinically well
<b>Breast:</b> Amputation; 2 years after recurrence in scar, metastases uterus, inoperable	3 years	Uterus normal, nodules in scar have disappeared
<b>Uterus:</b> 2 cases, inoperative, palliative curetting and cauterization	4 to 6 years	Clinically free from all evidences of carcinoma
<b>Intercostal:</b> Recurrence of breast cancer, inoperable	7 years	Completely receded, free from recurrence
<b>Uterus:</b> Inoperable, palliative curettement, cauterized	4 years	Well, uterus normal condition
<b>Maxilla:</b> Recurrence 3 months later. No treatment	3 months	Recurrence completely absorbed
<b>Broad ligaments:</b> Infiltrated, incomplete removal of uterus	7 years	No evidence of malignant growth
<b>Stomach:</b> Inoperable, metastases to mesentery (exploratory laparotomy)	9 years	Perfectly well
<b>Uterus:</b> Cervix, curetted, cauterization	11 years	Well, no evidence of tumor
<b>Uterus:</b> Curettement, cauterization	11 years	Well, no evidence of tumor
<b>Uterus:</b> Radical operation refused, epithelioma of cervix	22 years	Well, no evidence of tumor

10 remaining cases no definite data as to time given, patients well.

\* Rohdenburg, G. L.: Fluctuations in the growth energy of malignant tumors in man, with especial reference to spontaneous recession. Jour. Cancer Research, 1918 iii, 193-225.

In Table 2 a series of tests is shown which were made to ascertain the reliability of the NBM standard. If we consider that the figures given in Table 2 represent independent readings by three observers, and that the reaction for cholesterol is a progressive reaction in which the color formation may be slightly more rapid in some blood samples than in others (although no "very slow" specimens are included in this series) the element of error in the readings is very small, on an average of 3 mg. per 100 c.c.

The fact should be taken into account that some 1500 individual blood samples have thus far been tested by me and my two helpers which represents a total of between 80,000 and 90,000 readings, six tests being used for each sample and about ten readings for each test; consequently the opportunity to train our color vision has not been lacking.

#### SUMMARY

1. The test for cholesterol is not a diagnostic test, but furnishes information concerning cholesterol metabolism; it will therefore furnish information about the disturbances of cholesterol metabolism connected with cholelithiasis and carcinoma, for instance.

2. Cholesterol metabolism is influenced by the rate of basal metabolism; it was found to be inversely proportional to the latter in myxedema.

3. The reaction for cholesterol is a purely chemical reaction; technical procedures play a prominent part in the results obtained. Consequently the method of extraction and the conditions under which the color reaction takes place determine the values found in blood cholesterol determinations.

4. In clinical work, intended to promote our knowledge concerning the relation between the cholesterol content of the blood and pathologic conditions, a uniform method of procedure should be adopted for cholesterol determinations since this alone will insure comparable findings. A detailed account of the technic used in our determinations is given, because this technic is based on the determination of more than 1500 individual blood samples, which enabled us to recognize and eliminate many elements of error in the course of our work.

5. The cholesterol content of the blood is influenced by a number of factors, the nature of the diet, the rate of basal metabolism, radium

treatment, bacterial infection (ulceration, infectious disease), and hemorrhage. These factors should be duly considered in the clinical interpretation of blood cholesterol values. The cholesterol content of the blood is intimately related to lipid metabolism and the blood cholesterol can be influenced by dietetic measures.

6. It is known that the inefficiency of an individual organ can give rise to a particular type of metabolic disturbance; inefficiency of the thyroid results in myxedema, pancreatic inefficiency in diabetes.

7. There can be little doubt that an intimate relation exists between disturbances of the cholesterol metabolism and the lawless proliferation of cells that we observe in carcinoma, although the organ that is initially responsible for these disturbances has not yet been recognized.

8. The results obtained in the treatment of diabetes show what can be achieved in the face of organic inefficiency, and these results have been obtained by means of chemical investigations and by dietetic measures calculated to counterbalance the inefficiency of the pancreas, whereas the histologic study of the latter did not materially advance our knowledge in the treatment of the disease.

9. The fact that in a number of carefully controlled cases the tumors receded and the patients became "clinically well," although their conditions had been pronounced "hopeless," constitutes proof positive that the human body can wage a successful battle against malignant disease.

10. Investigations tending to elucidate the factors that connect lipid metabolism with malignant proliferation may enable us to do as much for cancer patients in the future as we can already do for diabetics. Massed evidence collected by means of uniform procedures will be needed to attain this end. Blood cholesterol determinations are a means by which our knowledge concerning lipid metabolism can be increased; hence they deserve a place in cancer research.

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# THE DETERMINATION OF THE LENGTH OF LIFE OF TRANSFUSED BLOOD CORPUSCLES IN MAN\*

WINIFRED ASHBY

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Whether transfused blood corpuscles live and function for any considerable length of time, or whether the beneficial results that have been observed to follow transfusion, outside the purely mechanical part of increasing the bulk of the depleted blood, are due to a stimulating effect on the hemopoietic function by the product of the broken down corpuscles is still an open question (Archibald, Crile, Hunter, Kimpton, Primrose, Robertson and Watson).

Marfels and Moleschott (1856) and Brown-Sequard (1867) studied the question of the length of life of blood corpuscles by injecting nucleated corpuscles into animals (bird and frog) having non-nucleated corpuscles, and watching for the disappearance of the nucleated corpuscles from the circulation of the transfused animal. It is now known that these results have no bearing on the question, as it was not blood destruction that was being studied but the elimination of foreign protein. The same objection holds good for any attempt to stain blood corpuscles with so-called vital stain and to reinject them, since there is no stain known that will hold without destroying the living quality of the corpuscles; therefore, in the stained corpuscle we are again dealing with a foreign body capable of more or less rapid removal than transfused blood.

Thus far the only satisfactory direct methods of attacking the problem of the length of life of transfused corpuscles have been those involving the study of the changes of the erythrocyte count following transfusion. Extensive work along this line, done on animals by Ward-Muller, Quincke, von Ott, and Hunter, was reviewed by Hunter in 1885 and 1886. Ward-Muller transfused dogs and produced a plethora. Two or three days afterward he found that the number of blood corpuscles corresponded closely to the number of the original corpuscles plus the transfused; a few days later the injected corpuscles, judged by the decrease in blood count, began to break down, and by the end of a few weeks all the injected corpuscles had disappeared. In order to produce the effect of a very slow transfusion Hunter injected blood intraperitoneally and found

\* Reprinted from *Jour. Exper. Med.*, 1919, xxix, 267-281.



that the blood count increased up to the second or third day, after which it gradually decreased and reached normal from the fourteenth to the twenty-sixth day, when 40 to 90 per cent of the total blood volume was injected. von Ott, in order to avoid the abnormal condition of plethora, removed from one-half to two-thirds of the blood from animals and replaced it with defibrinated blood. He noted a gradual fall in the blood count which reached a minimum from the nineteenth to the twenty-second day. From then on an increase took place which reached normal two weeks later. The lowest part of this curve would not, of course, represent the last of the transfused blood corpuscles but the point after which their destruction was surpassed by the regeneration of new corpuscles. The time that elapsed before the complete disappearance of transfused blood was something more than from nineteen to twenty-two days, a result which agrees well with the findings of the workers previously mentioned.

These and similar results, although they argue strongly in favor of the prolonged life of the red blood corpuscles after transfusion, have not been accepted as proof thereof, because they depend on the blood count uncontrolled by the volume of the blood. It is argued that the prolonged high blood count after transfusion may not represent an increased total number of corpuscles but an upset of long duration in the blood-volume-controlling factors, which results in a decrease in the fluid content of the blood and a consequent increased cell count.

Since the satisfactory determination of changes in the blood volume offers difficulties at present unsurmounted, it would seem that any method that could finally settle the question of whether or not the transfused blood corpuscles have any lasting existence in the blood stream must depend on some means of identifying the transfused corpuscles without changing it by stains, and so forth. It seemed possible to do this in man by making use of the blood groups that are so well defined there. In man there are four blood groups, based on the ability of the serum of one group to agglutinate the corpuscles of another (Sanford). The corpuscles of Group I are agglutinated by the serum of all other groups but its serum has no agglutinating properties. The serums of Groups II and III mutually agglutinate each other's corpuscles. Group IV serum agglutinates all other corpuscles, while Group IV corpuscles are not agglutinated by any serum. It follows then that a person in Group I may receive the blood of a person of any other group, and that the blood of a person in Group IV may be given to a person belonging in any of the other groups, since danger in transfusing blood of an unlike group arises only when there is agglutination of the incoming corpuscles, the transfused serum being too much diluted when mixed with the recipient's blood to produce any

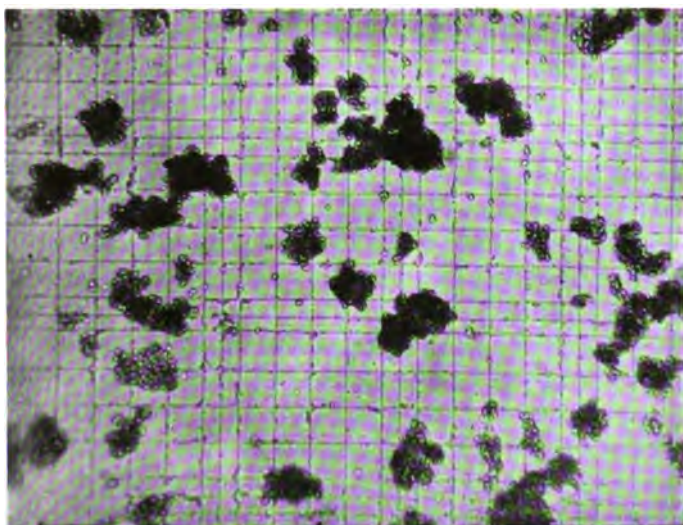


FIG. 247.—Microphotograph of the agglutinated blood of a person not transfused.

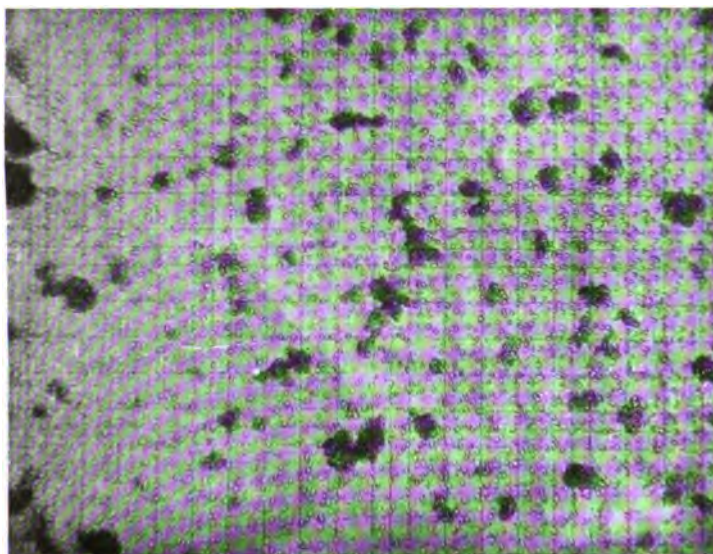


FIG. 248.—Microphotograph showing the clumps of agglutinated native corpuscles and the unagglutinated transfused corpuscles of blood of a person sixteen days after transfusion.

agglutination of his own corpuscles. Such transfusions, especially from the Group IV donor into the Group, I, II, or III recipient, are fairly commonly done in the Mayo Clinic. I have found that when a blood whose corpuscles are agglutinable is treated with a serum capable of agglutinating them, the agglutination may, by using sufficient serum, be made practically complete. The count of the few corpuscles lying between the clumps (Fig. 247) is usually from 0.5 to 0.7 per cent of the total blood count, but it may vary in different bloods from 0.03 to 3.4 per cent. When, however, unagglutinable corpuscles are mixed with agglutinable corpuscles, either by transfusion or in the test tube before the agglutinating serum is added, there is a very large number of free corpuscles present (Fig. 248) which appear in the proportion in which the two kinds of corpuscles are mixed. Since we have a means of separating the corpuscles of two groups that have been mixed by agglutinating the corpuscles of one group and leaving the corpuscles of the other unagglutinated, and since it is possible to transfuse a patient with a group other than his own, we may, by taking samples of his blood from time to time after transfusion and differentially agglutinating his own corpuscles, tell from the abnormal number of unagglutinated corpuscles present how long the transfused blood remains in the circulation.

### TECHNIC

Preliminary experiments were made with mixtures of bloods to determine the factors that it was necessary to control in order to obtain a technic which would give uniform results. Mixtures of corpuscles of known count were made; these were treated with the agglutinating serum, and after varying amounts of shaking and incubating, a count was made of the unagglutinated corpuscles in a red blood cell counting chamber. In this preliminary procedure a series of mixtures of blood to serum 1:1, 1:5.5, 1:11, 1:22, and 1:55 was made. Although the 1:1 mixtures gave numerous unagglutinated corpuscles, 1:5.5 did not give a consistently greater percentage than any of the mixtures in which a greater proportion of serum was used; therefore, the 1:22 mixture, which was adopted because of its adaptability to use in the white cell counting pipette, should secure a maximum agglutination. Shaking during incubation probably frees some of the unagglutinable corpuscles that might otherwise be caught in the

clumps of agglutinated corpuscles and thus increases the count of unagglutinated corpuscles in mixtures in which the unagglutinable corpuscles are present. Allowing the blood to stand in the ice box over night after incubation appears to give more uniform results. Slight differences in the length of time in the ice box caused no practical changes. Allowing the tubes to become warm after being in the ice box caused a decided increase in the count; thus it is advisable to keep each tube in the ice box until the count is to be made. Tubes may be thoroughly shaken to produce an even suspension before making a count without producing any increase in the unagglutinated corpuscles. Ten minutes' shaking in a mechanical shaker with glass beads in the tube increases the count of the unagglutinated corpuscles only 1 to 2 per cent of the total blood count, and here heat rather than the shaking is probably the factor that causes the increase. If the unagglutinated corpuscles are so thick that the count cannot readily be made, it is possible to make a dilution with cold serum. It is not advisable to use normal salt solution as that increases the count. Partly as a result of this preliminary work and partly for the sake of uniformity, the following technic was adopted:

Blood is taken from the ear in a white cell counting pipette to the 0.5 mark, the pipette is then filled to the 11 mark with the agglutinating serum to which a 4.4 per cent citrate solution has been mixed in the proportion of 20:1, and the whole is expelled into a small test-tube and shaken, thus giving a 1:22 mixture of blood and citrated serum. This mixture is incubated at 37°C. for forty minutes with thorough shaking every ten minutes and is left in the ice box over night. The mixture is then thoroughly shaken and a drop of it is placed in a red blood cell counting chamber and a count of the unagglutinated corpuscles is made; 160 squares in each of two chambers are counted, the average is taken, and the count multiplied by  $\frac{1100}{2}$  to give the number of unagglutinated corpuscles per cubic millimeter of blood. A tube containing the blood of a person who has not been transfused is always used to control the effectiveness of the serum, and serum from the same person is used for agglutinating throughout a set of experiments.

#### DIFFERENTIAL AGGLUTINATION IN VITRO

*In vitro* experiments were done to establish whether or not the results obtained by agglutinating the agglutinable corpuscles in a mix-

ture of unagglutinable and agglutinable corpuscles were quantitative, and to determine whether, in such a mixture, the number of unagglutinable corpuscles counted is equal to the number actually present or whether it is some fraction of that number. To show the accuracy of the technic under absolutely uniform conditions with the same blood and serum and simultaneous shaking and incubation, two tests were made of each of a series of mixtures with different pipettes and the results compared (Table 1).

These figures show a degree of accordance between each of two distinct tests which leaves no doubt as to their quantitative character.

In order to compare the number of unagglutinated corpuscles with the known number of agglutinable corpuscles present, mixtures of a Group IV blood with a Group II blood were made by the drop method in such proportions as 1:30, 1:15, 1:10; the same capillary pipettes were used throughout. Samples of these mixtures, which had been thoroughly shaken, were diluted in the white cell counting pipette with the Group IV serum, after which the usual technic was followed. Two agglutinations were made from each mixture and the count of the unagglutinated cells was averaged after subtracting the number of unagglutinated corpuscles found in the pure Group II blood, which in this instance was rather high, being 119,900 per c.mm. The number thus obtained was compared with the number of the Group IV corpuscles computed to be present, and found by dividing the count of the Group IV blood used by the fraction which it composed of the whole mixture. The results are shown in Table 2.

Through a wide range of mixtures the counted number of unagglutinated corpuscles approximated closely the number of unagglutinable Group IV corpuscles computed to be present.

TABLE 1

Proportion of Group IV corpuscles mixed with Group II corpuscles	Red blood cell count of mixture	Unagglutinated corpuscles in		Tube 1 minus Tube 2	Percentage of difference based on total blood count
		Tube 1	Tube 2		
1:30	4,880,000	235,400	209,000	26,400	0.58
1:25	4,870,000	249,700	228,800	10,900	0.22
1:20	4,840,000	335,500	325,600	9,900	0.20
1:15	4,800,000	474,200	464,200	6,600	0.14
1:10	4,710,000	578,600	566,500	12,100	0.26
1:5	4,500,000	894,300	887,700	6,600	0.15
Average percentage of error.....					0.25

TABLE 2

Proportion of Group IV corpuscles mixed with Group II corpuscles	Unagglutinated corpuscles per c.mm. minus 119,900	Calculated No. of Group IV corpuscles per c.mm.
1 : 30	127,370	137,000
1 : 15	228,570	267,000
1 : 10	391,600	388,100
1 : 6	572,773	610,000
1 : 4	803,559	854,000
1 : 3	1,035,320	1,067,500

EVIDENCE THAT THE UNAGGLUTINATED CORPUSCLES OBSERVED AFTER TRANSFUSION ARE THE TRANSFUSED CORPUSCLES

Before the abnormal increase of unagglutinated corpuscles found in the blood of Group I, II, and III patients transfused with Group IV blood could be assumed to be due to the presence of the transfused blood, it was considered necessary to run control experiments covering two points, (1) to see that this increase in count of unagglutinated corpuscles does not appear when a patient with blood of an agglutinable group is transfused with blood of the same group, and, therefore, that the appearance of unagglutinated corpuscles is not some non-specific reaction incident to the introduction of foreign blood, and (2) to see that the appearance of the unagglutinable corpuscles is not due to a reaction of the transfused Group IV serum on the recipient's native corpuscles.

It was also of interest to note, in as far as it was practicable with our insufficient knowledge of the blood volume, whether there was any correlation between the amount of blood transfused and the number of unagglutinated corpuscles which appear in the circulation following transfusion with unagglutinable blood. That the increase in unagglutinable corpuscles does not appear except when unagglutinable blood is transfused is shown in the following results:

Of four patients who were transfused with blood of a like group, one gave 91,300 per c.mm. unagglutinated corpuscles before transfusion and 42,900 per c.mm. after transfusion, when 200 c.c. of blood were transfused. In the 3 other cases, when 500 c.c. were transfused, 51,700, 52,800, and 8800 per c.mm. of unagglutinated corpuscles respectively were counted. As the agglutination with no transfusion has varied within the limits of from 0.03 to 3.4 per cent of the blood count, these figures are well within normal limits.

On the assumption that the appearance of unagglutinated corpuscles might be due to the transfused serum, the following experiment was done. During a transfusion on a Group II patient which lasted less than thirty minutes and in which 500 c.c. of citrated Group IV blood were transfused, samples of blood were taken from the ear, one after 300 c.c., and one after 500 c.c. of blood had been given. A control had been taken immediately before the transfusion. The results obtained by agglutinating with Group IV serum were: before transfusion 41,690 unagglutinated corpuscles per c.mm., after transfusion of 300 c.c., 269,000 unagglutinated corpuscles per c.mm., and after transfusion of 500 c.c., 478,390 unagglutinated corpuscles per c.mm. Samples of blood taken before transfusion, both citrated and uncitrated, in this case and in others gave no increase in the unagglutinated corpuscle count when mixed with Group IV serum in the proportion of 1:22 and incubated for twenty-four hours. It would seem that if *in vitro* Group IV serum does not affect the agglutinability of Group II corpuscles during twenty-four hours at body temperature in more than 100 times the concentration in which it appears in the recipient's body, the immediate increase in unagglutinable corpuscles obtained during transfusion is not due to a reaction of any constituents of the transfused serum on the recipient's native corpuscles.

Whether or not the unagglutinated corpuscles appear in numbers proportional to the amount of blood transfused is shown in 7 patients, of whom 6 were transfused with Group IV blood and one was a Group I patient who was transfused with Group III blood. The count of the unagglutinated corpuscles was compared with a computed figure obtained from the amount of blood transfused, the body weight, and a factor common to the series. If the correction is omitted which would be necessary if differences exist in different persons in the proportion between blood and body weight, concerning which unfortunately we have no satisfactory data, it may be assumed that the number of unagglutinated corpuscles which appear should be directly as the amount of blood transfused and inversely as the body weight. Taking  $x$  as the common unknown factor in Case A (Table 3), in which the amount of blood transfused was 200 c.c., the body weight 133.5, and the count of unagglutinated corpuscles 220,000, we have

$$220,000 = \frac{200}{133.5} x$$

Then by solving for  $x$  whose value is 146,850 and substituting in a similar equation in Case B in which the amount of blood transfused was 500 c.c. and the body weight 151 pounds, a computed figure will be obtained, which may be called  $y$ , for the number of Group IV corpuscles which should be present per c.mm. Thus

$$y = \frac{500}{151} \times 146,850$$

$$y = 486,258$$

If we continue this process through the series, computed figures are obtained which give a basis of comparison of the results obtained in different cases. A comparison of these computed figures, with the counted number of corpuscles, is given in Table 3. If due allowance is made for the inherent factor of error in the computed figures it will be seen that the degree of agreement between these two sets of figures indicates a quantitative relation between the amount of blood transfused and the number of unagglutinated corpuscles which appear in the circulation after transfusion. The weight at the time of transfusion was used in all instances except in Case B in which the patient could not be weighed.

TABLE 3

Case No.	Reason for transfusion	Weight lbs.	Amount of blood transfused c.c.	Calculated No. of Group IV corpuscles per c.mm.	Counted unagglutinated corpuscles per c.mm.
A	Preparatory to operation.	133.5	200		220,000
B	Pernicious anemia. Transfused 20 days previously with 500 cc. of Group IV blood.	151 (normal)	500	486,258	551,000
C	Hemorrhage following Kraske operation.	96	500	764,843	698,000
D	Pernicious anemia. Transfused 19 days previously with Group IV blood. The initial count of unagglutinated corpuscles was 10 per cent of the blood count.	96	500	764,843	980,000
					700,000 (minus initial count)
E	Anemia.	135	500	543,888	409,200
F	Hemorrhage following hysterectomy.	138	1,200	1,276,956	1,412,400
G	Anemia (infant).	20.5	250	1,790,853	1,175,900



# EVIDENCE OF THE PROLONGED EXISTENCE OF TRANSFUSED BLOOD CORPUSCLES

Application of this technic was undertaken for the purpose of determining whether or not transfused blood lives in the circulation, and specimens of blood of patients of an agglutinable group transfused with Group IV blood were taken before, and at short intervals after transfusion. These specimens were examined for the persist-

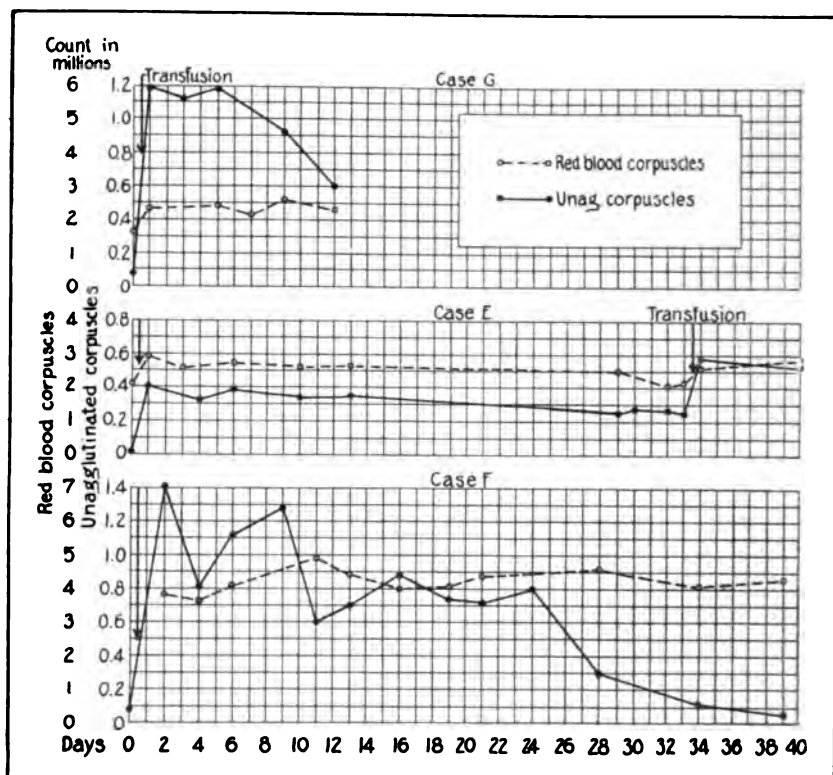


FIG. 249.—The rate of change in the number of transfused corpuscles per cubic millimeter and the accompanying changes in the total blood count.

ence after transfusion of abnormal numbers of unagglutinated corpuscles. The protocols of Cases G, E and F give the counts of unagglutinated corpuscles and a simultaneous study of the total blood count (Fig. 249). These figures represent the average of two pipettes. The unagglutinated corpuscles of the normal untransfused Group II individual who was used as a control varied through the experiments from 0.5 to 0.7 per cent of the total blood count.

*Case G.*—A fat infant, aged 17 months, weighing 20.5 pounds and belonging to Group II had a low blood count. A diagnosis of secondary anemia had been made Sept. 20, 1918. The red blood cells were 1,660,000; the unagglutinated corpuscles were 54,400 per c.mm. A transfusion was done of 250 c.c. of citrated Group IV blood.

Sept.	21.	Red blood corpuscles	2,375,000; unagglutinated corpuscles	1,175,000 per c.mm.
"	23.	"	"	1,107,700 " "
"	25.	Red blood corpuscles	2,380,000; "	1,192,400 " "
"	27.	"	"	2,260,000; "
"	29.	"	"	2,570,000; unagglutinated corpuscles 9,933,900 per c.mm.
Oct.	2.	"	"	2,280,000; " 602,250 " "
"	4.	Sent to the hospital with an attack of influenza.		
"	7.	Died.		

*Case E.*—A Group II individual, aged 32, had a secondary type of anemia, possibly from hemorrhage due to piles. The patient's normal weight was 160 pounds, the present weight was 135 pounds. Oct. 1, 1918, the red blood cells were 2,100,000; the unagglutinated cells were 1,100 per c.mm.

A transfusion was done with 500 c.c. of Group IV blood.

Oct.	12.	Red blood corpuscles	2,820,000; unagglutinated corpuscles	409,200 per c.mm.
"	14.	"	"	2,550,000.
"	15.	Unagglutinated corpuscles		318,000 " "
"	17.	Red blood corpuscles	2,705,000; " "	390,700 " "
"		Mild attack of influenza.		
"	21.	Red blood corpuscles	2,600,000; " "	333,700 " "
"	24.	"	"	2,660,000; " "
"	25.	Went home for two weeks.		
Nov.	9.	Red blood corpuscles	2,510,000; unagglutinated corpuscles	251,020 per c.mm.
"	10.	"	"	260,700 " "
"	12.	Red blood corpuscles	2,105,000; " "	258,720 " "
"	13.	"	"	2,185,000; " "
"		A transfusion was done of 500 c.c. of Group IV blood.		
"	14.	Red blood corpuscles	2,625,000; unagglutinated corpuscles	585,200 per c.mm.
"	20.	"	"	2,760,000; " "

*Case F.*—A woman, aged 35, whose normal weight was 140 pounds, and present weight 138, was operated on for fibroid of the uterus. Sept. 21, 1918 the agglutinated cells were 88,000 per c.mm.; the blood count could not be obtained; 700 cc. of Group IV blood were given because of severe hemorrhage; the hemorrhage continued and an additional 500 cc. of Group IV were given.

Sept.	23.	Red blood corpuscles	3,800,000; unagglutinated corpuscles	1,412,400	per c.mm.
"	25.	"	"	807,400	"
"	27.	"	"	1,130,800	"
"	30.	"	"	1,293,800	"
Oct.	2.	Red blood corpuscles	4,920,000;	590,700	"
"	4.	"	"	704,000	"
"	7.	"	"	870,100	"
"	10.	"	"	737,000	"
"	12.	"	"	702,900	"
"	15.	"	"	796,400	"
"	19.	"	"	299,200	"
"	25.	"	"	118,800	"
"		"	"	51,700	"

The greater irregularities in the count of unagglutinated corpuscles in this protocol are due to the fact that the patient's blood often clotted the Group IV serum with which it was mixed. This tendency was overcome later by increasing the strength of the citrate solution from 2 per cent to 4.4 per cent.

It will be noted in these cases that in each instance before transfusion there was an initial count of unagglutinated corpuscles which came within the limits of the counts found in other untransfused persons, while after transfusion there was a very great increase in unagglutinated corpuscles. In Case F, the patient who had had a severe hemorrhage and in whom the amount of blood transfused was great, this increase amounted to more than 30 per cent of the total blood count; in Case G in which the initial blood count was extremely low and the amount of blood given in proportion to the body weight was also great it amounted to nearly 50 per cent of the patient's blood count. The increase was maintained for a long time with a surprisingly slow fall. In Case G, in which the patient died five days after the last count was taken, only half the number of unagglutinated corpuscles which appeared after transfusion had disappeared in twelve days; in Case E the condition remained on a level notwithstanding a slight attack of grippe; there was no marked decrease in the original number of unagglutinable corpuscles after thirteen days, and in thirty-three days there was only a 37 per cent fall; in Case F, that of a comparatively normal patient who made an excellent recovery from operation, there was a marked decrease in unagglutinated corpuscles between the twenty-fifth and twenty-eighth days, and the agglutinability of the patient's blood may be considered to have approximately reached normal by the thirtieth day. In all cases the unagglutinated corpuscles, as long as they were present in considerable numbers, appeared to be in good condition.

I have shown that this differential agglutination reaction is a constant and quantitative one and that the unagglutinated corpuscles are present in numbers equal to the unagglutinable corpuscles admixed, so that unless some action takes place in the body that does not take place in the test-tube, the counts of unagglutinated corpuscles after transfusion may be assumed to be a quantitative indicator of the number of transfused corpuscles present. Since the unagglutinated corpuscles appear after transfusion in numbers proportionate to the amount of unagglutinable blood transfused, since they do not appear when agglutinable blood is transfused, and, moreover, since they are not caused by any effect of the Group IV serum on the recipient's corpuscles, it seems safe to assume that these unagglutinated corpuscles are the transfused corpuscles and that their number is a quantitative indicator of the amount of transfused blood present in the recipient's

circulation. It must follow then that the prolonged appearance of unagglutinated corpuscles in the blood stream of these transfused patients can only mean that the transfused corpuscles existed for a long time in the circulation, and it seems that they not only existed but functioned

In considering these results, the question of to what extent they apply to the more usual condition when the patient is transfused with blood from a person in his own group, immediately arises. Since the peculiarities which are brought out in blood grouping are probably peculiarities which will also be found in all the cells of the body, we may be able to turn to other tissues for light on this point. In this connection Masson's work in skin grafting is of interest.

"In all patients requiring skin grafting who were under my care during the past year, the blood of the donor, as well as that of the recipient, has been tested for agglutination. The results have been very interesting and instructive, and I feel sure will add a great deal to the popularity of the use of the isograft. . . . I have tested the principle with the three varieties of grafts, and am satisfied that blood grouping is just as important for good results in skin grafting as it is necessary in transfusion, and that it is governed by the same principles. While the results are not positive, nevertheless, I have never had a skin take which was removed from a donor whose red blood corpuscles were agglutinated by the serum of the patient. The results in all other cases have been very satisfactory, almost, if not entirely, equal to autodermic grafting."

It would seem probable, if further investigation bears out the above results with skin grafts, that the results obtained in studying the length of life of transfused Group IV corpuscles in a recipient of another group hold for the life of the corpuscles of any group transfused into the recipient of a like group, and that it is even probable that these results hold for the length of life of the native corpuscle.

Since my results show that there is no immediate breaking down of transfused cells which could cause a stimulation of the bone marrow, and since it is more probable, as suggested by Lindeman, that when there is a stimulation of the bone marrow following transfusion it is due to improved metabolic conditions of the bone marrow cells, brought about by the larger number of corpuscles in the blood, it would seem, on the surface, that the logical procedure in transfusion would be to push the transfusions until a normal blood count was attained, making the time interval between transfusions only long enough to allow the fluid content to establish itself. This would be indicated by the rise in the blood count which takes place a day or two after transfusion.

## CONCLUSIONS

1. It is possible in mixtures of corpuscles of different groups to separate the corpuscles practically quantitatively by treating with a serum that agglutinates the corpuscles of one kind, leaving the others unagglutinated.

2. After a recipient has been transfused with blood of a group other than his own, specimens of his blood treated with a serum that will agglutinate his own corpuscles but not the transfused corpuscles show unagglutinated corpuscles in large numbers.

3. These unagglutinated corpuscles which appear in the recipient's blood after such a transfusion are the transfused corpuscles and their count is a quantitative indicator of the amount of transfused blood still in the recipient's circulation.

4. The life of the transfused corpuscle is long; it has been found to extend for thirty days and more. The beneficial results of transfusion are without doubt not due primarily to a stimulating effect on the bone marrow, but, it is reasonable to assume, to the functioning of the transfused blood corpuscles.

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## PRACTICAL CONSIDERATIONS OF THE DANGERS ASSOCIATED WITH BLOOD TRANSFUSIONS\*

J. DE J. PEMBERTON

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Nothing tends to bring a therapeutic measure more quickly into disrepute than the abuse of its employment. As a therapeutic agency blood transfusion has risen to a position of recognized eminency and, as a precaution against its too frequent employment in cases of questionable indications, a discussion of the principal dangers and complications attendant on and resulting from its use seems in place.

The medical profession was stimulated by the experiments and writings of Crile, Carrel, Guthrie, Landsteiner, Moss, Brem, and others, to the realization of the enormous therapeutic possibilities in the operation of blood transfusion, and since then, by the efforts of hordes of workers, innumerable methods and modifications have been devised. At first, on account of the technical difficulties encountered, the operation was uncertain and time-consuming, its practice was necessarily limited to a few skilled surgeons with specially devised instruments and specially trained corps of assistants, and its employment was restricted to specially selected cases. But today, after repeated modifications, the technic is so simplified that blood transfusion may be successfully accomplished by the least skilled operator, and naturally the measure is advocated in ever widening fields.

We have recognized the dangers associated with blood transfusion, but in our eagerness to point out the particular advantages of some special method, or to exploit a pet theory with regard to its therapeutic value in some particular disease condition, the dangers have, to a certain extent, been lost in the background. While the occasional transfusion is successfully performed without preliminary blood tests, the operator whose experience has been at all extensive will not risk such a procedure unless under the most urgent circumstances.

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The principal dangers associated with the transfusing of blood from one person to another are: (1) The introduction of air and blood clots as emboli, (2) acute dilatation of the heart, (3) the transmission of infection, and (4) agglutination or hemolysis of the donor's corpuscles.

Air introduced into the circulatory system may prove dangerous. Experimentally this may be demonstrated by pumping a large volume of air into the vein of an animal. Clinically in extensive surgical operations on the neck, when an opening in a vein is for a time unrecognized, suddenly the condition of the patient, without apparent cause, becomes grave; cyanosis and dyspnea develop, the pulse becomes weak and rapid, and death quickly follows. Necropsy reveals extensive air emboli in the heart and lungs. Air in the circulatory system to be dangerous, however, must be present in large quantities, for in the course of operations, especially on the neck, small quantities of air can frequently be demonstrated in the vein without producing any effect on the patient. But today, with our simple method of transfusion (citrate method), this danger of introducing into the circulation sufficient air to produce any ill effect can be easily avoided. By the employment of a small caliber needle for insertion into the recipient's vein and by allowing the flow of blood to be under low pressure, the introduction of blood clots of sufficient size to produce harm can be absolutely prevented.

The danger arising from an acutely dilated heart demands constant recognition. In the aged with marked arteriosclerosis, in the extreme anemic with the resultant myocardial impairment, and in others with suspected cardiac lesions, the quantity of blood injected must be limited and caution must be exercised to avoid the too rapid loading of the right heart.

The possibility of transmitting disease from the donor to the recipient in the course of blood transfusion has not received the attention in the literature on the subject that it obviously deserves. Syphilis, of course, is the most likely disease to be conveyed in this manner, and most writers in discussing the subject are satisfied by cautioning that all donors must have a negative Wassermann. While the recorded number of patients who have acquired syphilis in this manner is indeed small, when we consider the prevalence of the infection and our admittedly inadequate means of detecting its presence, this possibility immediately demands wider recognition. Syphilis is one of the most wide-spread of all infectious diseases. Accurate data

with regard to its prevalence in the general population are not obtainable. Syphilologists, basing their opinion on the study of statistics from different groups or classes of people, estimate that from 10 to 18 per cent are syphilitic. For instance, Vedder found 20 per cent infected with syphilis among the class of men from twenty-five to thirty years of age from which the army is recruited. He also estimated that about 5 per cent of the young men in our colleges are syphilitic. Syphilologists agree that the Wassermann test cannot be considered as an infallible test in the diagnosis of syphilis. Its accuracy varies with the skill and experience of the serologist. Stokes has stated that a negative Wassermann, while rare in secondary syphilis, occurs in 35 per cent of syphilitics in the later stages of the disease and in all syphilitics during the first few days of the primary lesion.<sup>8</sup> "Repeated negative Wassermann tests may be obtained in persons in whose blood the *Spirochaeta pallida* can be demonstrated by animal inoculations."<sup>9</sup>

In the light of our present knowledge of syphilis, the possibility of a patient being infected cannot be conscientiously ruled out except after a thorough examination by a competent syphilologist in conjunction with a negative Wassermann. In accepting a professional or a volunteer donor with only a negative Wassermann label attached, the responsibility of the operator becomes exceedingly heavy and immediately his first thought should be: Are the indications for transfusion so urgent in character as to warrant the risk attendant on this procedure? Are we justified in using the blood of a professional donor unless he is subjected to a most rigid examination? For example, the transfusion of a young woman who has become moderately anemic from excessive or prolonged menstruation without any evidence of malignancy will tend to check the bleeding and overcome the anemia quicker than any other known therapeutic measure. But unless a suitable donor can be obtained from among her relatives general supportive measures, such as rest in bed, fresh air, nourishing food, with tonics of iron, arsenic, and the like, should be advocated rather than transfusion.

There are many instances in which the condition of the patient is so critical and the indication for transfused blood is so apparent, however, as in a case of acute hemorrhage, that the risk of transmitting syphilis should be of secondary importance. There are other diseases in which the immediate condition is less critical, but in which the value of transfusion is equally apparent, as in the anemic patient



preliminary to operation for carcinoma of the gastro-intestinal tract. All diseases cannot be classified according to the relative urgency with which transfusion is indicated; each case must be judged by itself.

The chief immediate danger in blood transfusion is the introduction of incompatible blood into the vein of the patient, that is, blood in which the cells of the donor are agglutinable by the serum of the patient; immediate agglutination of the transfused corpuscles occurs. Isohemolysis may also be present so that there is destruction of the red blood cells with the liberation of the hemoglobin. Clinically we detect this by the severe reaction through which the patient passes and by the finding of hemoglobinuria, increased urobilin, and phagocytosis of the red blood cells. The gravity of this danger depends on the extent of the destruction. In a series of 1092 blood transfusions at the Mayo Clinic there were 12 instances in which severe reactions resulted from the massive destruction of red blood cells. In the 9 cases in which regrouping of the bloods of the patient and donor was possible an error was discovered in the initial blood test (usually a clerical error in recording the group). The clinical picture of these reactions is typical. They occur early, after the introduction of 55 c.c. or 100 c.c. of blood; the patient first complains of tingling pains shooting over the body, a fullness in the head, an oppressive feeling about the precordium, and, later, excruciating pain localized in the lumbar region. Slowly but perceptibly the face becomes suffused a dark red to a cyanotic hue; respirations become somewhat labored, and the pulse rate, at first slow, sometimes suddenly drops as many as from 20 to 30 beats a minute. The patient may lose consciousness for a few minutes. In one-half of our cases an urticarial eruption, generalized over the body, or limited to the face, appeared with these symptoms. Later the pulse may become very rapid and thready; the skin becomes cold and clammy, and the patient's condition is indeed grave. In from fifteen minutes to an hour a chill occurs, followed by high fever, a temperature of 103° to 105° and the patient may become delirious. Jaundice may appear later. The macroscopic appearance of hemoglobinuria is almost constant.

Fortunately, in most instances the reaction becomes manifest after the introduction of 50 c.c. to 100 c.c. of incompatible blood, and if the symptoms are recognized and the operation quickly concluded, the patient's condition, while obviously grave, will probably not prove

fatal. If the symptoms are not early recognized and interpreted as danger signals, however, and if 500 c.c. or more of incompatible blood are injected into the circulation, fatal results are to be expected. Happily these reactions are absolutely preventable by preliminary blood tests performed by competent laboratory workers. The accuracy of these tests is well substantiated by the fact that in more than 2500 transfusions in our clinic there has not been a single group reaction when the bloods of the donor and recipient were properly tested before the operation. The necessity of a preliminary test cannot be over-emphasized, and in no instance except in the utmost urgency, as in an acute massive hemorrhage when the life of the patient is in the balance, and time does not permit the testing of a donor, are we justified in using a donor whose blood has not been previously grouped.

Such contingencies can be avoided to a large extent, however, especially in large surgical centers, where emergency transfusions are most likely to occur, by maintaining a list of prospective donors from among hospital attendants who have been previously tested and whose blood has been found suitable (Group 4) for any recipient; that is, whose corpuscles are not agglutinable by the serum of any others. If an untested donor is employed, extreme caution should be observed, allowing the first 100 c.c. of blood to flow into the vein of the recipient very slowly, consuming at least five minutes. And if any untoward symptoms develop, the transfusion should be immediately concluded and another donor secured.

The operator should be conversant with all the dangers associated with the transference of blood from one person to another. He should exercise judgment in advising the procedure, taking into account the urgency of the indications, and he should be conscientious in the selection of the donors, employing only those who have recently been subjected to a physical examination and a Wassermann test. The application of this valuable therapeutic measure must not be undertaken without a careful consideration of all the dangerous complications that may follow. The procedure is very often considered only a simple intravenous medication or a minor operation, while in reality its potential dangers place it with the major operations.

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## DIAGNOSTIC METHODS IN THE ANEMIAS\*

A. H. SANFORD

Biermer's revival of interest in the disease described by Addison gave us the classical description of that complex of symptoms whereby the diagnosis of progressive pernicious anemia is made today. Ehrlich pointed out a certain type of blood picture in this anemia which has not been changed by subsequent minor improvements in staining methods.

Barker and Sprunt, in recent papers, have used the expression "so-called pernicious anemia" in referring to this condition. Our conception of the misnomer in the term applied to the Addison-Biermer type of anemia applies to its being called "primary anemia." As yet there has not been established an etiologic factor for this condition which is primarily located in the hematopoietic system. We may conjecture that some unknown cause is perversely accelerating the normal rate of blood destruction and coincidentally overstimulating the blood-forming organs to the point of exhaustion. However, if some known etiologic factor produces a "color-index" of  $1 +$  and an anemia that finally terminates fatally, clinicians are prone to discard the diagnosis of the condition as "true idiopathic progressive primary pernicious anemia". But as soon as all of the factors concerned with the production of this syndrome have been found, we shall probably recognize that the anemia, though progressive and malignant, is not primary, but is truly secondary to some other condition. This again is mere conjecture, for modern diagnostic methods throw no light on this point.

It is unnecessary to reiterate the description of the familiar findings in the Addison-Biermer type of anemia and of those points that differentiate it from some of the other rare and somewhat obscure diseases in which anemia is one of the cardinal symptoms. It

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might be mentioned at this time, however, that either this particular disease is on the increase or else we have become more keen in the diagnosis of the condition, as it is an undoubted fact, heard in all sections of the country, that we are seeing more cases of "pernicious anemia" than we did ten or fifteen years ago.

In the differentiation of diseases in patients who complain chiefly of weakness, who have anemia of obscure origin, with color indices about or slightly above 1, with icteric tinges to their skins, or histories of slight chronic jaundice, with spleens that may or may not be palpable, there are certain diagnostic tests that we have made use of in the past few years that have proved to be of some real value. In no single instance have all these procedures been employed nor has any one single method been used for all the patients whom we have seen at the Mayo Clinic. However, the following procedures may be of benefit in adding evidence to the ordinary blood findings and to the clinical history:

1. Analysis of the gastric contents by means of the test meal and a subsequent x-ray examination of the stomach.

2. A careful neurologic examination, and examination of the eye grounds.

3. Tests for the fragility of the erythrocytes.

4. Detection of evidences of blood destruction by determinations for urobilin and urobilinogen in the stool, or preferably in the duodenal contents.

5. Serologic tests for syphilis.

6. Examination of stools for parasites.

7. Inspection of the mouth, especially the tongue, and a thorough examination of the teeth and tonsils. The possibility of chronic sepsis originating here, and of foci of infection in other parts of the body, should have general consideration.

Among the simple clinical laboratory procedures that are not of themselves diagnostic but which add to the evidence that the disease under consideration is pernicious anemia is the finding of achlorhydria in the contents of the stomach by the ordinary test methods with the Ewald meal. This test should usually be followed by x-ray examination in order to exclude the possibility of malignant neoplasm as a cause for the achlorhydria. Practically always in pernicious anemia there are no free acids present; the total acidity amounts to about 6 or 8. The x-ray examination of the stomach in pernicious anemia gives a negative result.

The nervous symptoms of pernicious anemia are known to resemble the symptoms of *tabes dorsalis* in many respects. A careful neurologic examination, however, will bring out the differentiating points: the changes that take place in the cord are not only in the posterior columns but in the lateral bundles as well. The findings as usually reported by the neurologist are those of "subacute combined sclerosis." Woltman has pointed out, in a pathologic study of the brain in pernicious anemia, that there are definite degenerated areas in the medullary portions of the cerebrum similar to those found in the posterior and lateral fupiculi. The gray matter is also by no means immune from the destructive process and at times degeneration around the pyramidal cells on the margin of the gray matter which may lead to their ultimate destruction is fairly demonstrable. It is considered that the clinical manifestations such as somnolence, apathy, and delirium are possibly in a measure dependent on such lesions although the chief cause of the symptoms is probably the toxin itself. Subacute combined sclerosis is also found in other conditions such as in leukemia. Addison's disease, severe secondary anemia, nephritis, posterior sclerosis, pelagra, tuberculosis, syphilis, chronic alcoholism, lead phosphorus, or arsenic poisoning, or in other forms of chronic intoxication. It still remains that if the patient presents the classical picture of pernicious anemia without any signs or history of the diseases just mentioned, a neurologic examination will add much confirmatory data. In the superficial sensibility, tactile, pain, and thermal reactions are usually diminished in a large percentage of instances. The vibration and joint senses are both greatly impaired. These deep sensations are elicited by means of a low pitched tuning fork applied over bones or joints. As has been mentioned, signs of apathy are usually present when there is advanced change in the nervous system in pernicious anemia; there may be also true psychoses or other impairments of mentality. Unlike in *tabes dorsalis* the reflexes, due to the blocking that takes place in the lateral bundles, often may be increased rather than diminished. The early case of pernicious anemia with only an involvement of the posterior columns may show the diminished reflexes of *tabes*, but ordinarily a positive Babinski and increased patellar reflexes are present. Lack of coördination may be such that the person cannot touch two forefingers together with his eyes closed or touch the tip of his nose without over-reaching. Instability in standing and a well marked Romberg, if the patient has strength

to support himself, characterize the advanced stages. The gait may be ataxic although later, unlike in *tabes dorsalis*, it may become both spastic and ataxic. In a recent study, from the standpoint of the nervous system alone, of 150 of the cases of pernicious anemia at the Mayo Clinic, Woltman found evidence of nervous tissue disintegration in 80 per cent of moderately advanced types; this is in accord with the figure of Minnich who demonstrated that 77 per cent of the cases of pernicious anemia are associated with lesions of the spinal cord. Subjectively, some form of paresthesia such as numbness and tingling is rarely absent. Objectively, the most striking disturbance is in the altered reflexes, and the disturbance of vibration and joint sensibilities. Minnich emphasizes the point that the examination of the nervous system is of inestimable value in differentiating pernicious anemia and other anemias. The frequency of cord changes in pernicious anemia is not generally appreciated by clinicians. As part of the neurologic examination, or at times preferably as a report of the eye specialist, very important and characteristic findings may be obtained from an ophthalmoscopic examination of the retina. The description of the retinal changes that occur in pernicious anemia is tersely and adequately dealt with in Knapp's recent book, "Medical Ophthalmology."

"In severe anemias multiple hemorrhages and small white degenerative foci are observed in the retina. They are important from a diagnostic standpoint, from the great regularity with which they occur. This is particularly true in the progressive pernicious type of anemia where they occur in 50 per cent of the cases. Some claim that in the acme of the disease they are practically constant. . . . Small hemorrhages, followed after a few days by multiple ones, then very large extravasations of blood, are very characteristic and indicate a severe prognosis." Similar ophthalmoscopic pictures occur in other conditions. Knapp mentions the anemia of *Ankylostoma duodenale* and *Bothriocephalus latus* infections which, by some observers, have been considered as merely instances of pernicious anemia with known etiology. The retinitis in the cachexia of malignancy, and in all forms of chronic intoxications, is very similar but it is claimed that there are distinguishable differences in the picture.

The physician may be puzzled to differentiate pernicious anemia and some other condition causing blood destruction and an attendant icteric tinge to the skin and sclera; especially may this apply to hemo-

lytic jaundice. The latter rare disease is characterized by anemia. The jaundice is of hematogenous origin and is usually supposed to be due to the setting free of coloring matter of the blood through the destruction of erythrocytes. The spleen is enlarged in the later stages of the disease. The anemia is usually of the secondary type, although cases are recorded in which the blood picture was practically that of pernicious anemia in those cases of hemolytic jaundice that go on to a fatal termination. The simple laboratory test for the degree of resistance of the corpuscles in hypotonic salt solution may be an aid in the differentiation in this type of case. A number of methods have been advocated; we have found that a modified Ribierre test is very convenient and quickly furnishes the desired information. The necessary apparatus consists of a double-row twelve-hole rack full of Wassermann tubes, freshly made sodium chlorid solution of exactly 0.5 per cent strength, distilled water, a pipette with a small tip for diluting the salt solution with the distilled water by the drop method, and an all glass syringe for obtaining the blood by venipuncture. The test is "set up" by placing 25 drops of 0.5 per cent sodium chlorid solution in the first tube, 24 drops in the second, and one less in each succeeding tube than is in the one immediately to the left of it. No distilled water is added to the first tube, but in the second tube one drop, in the third tube two drops, and so on, so that the total number of drops of sodium chlorid solution and distilled water is twenty-five. Blood is obtained from the person's veins by venipuncture and one drop of blood is added to each tube of hypotonic salt solution. At the same time, for control, there is placed in a similar number of tubes blood from a person without jaundice. A normal person will show a slight hemolysis of his red cells in 0.40 per cent or 0.42 per cent sodium chlorid solution. This is evidenced by a slight tingeing of the supernatant fluid after the cells have settled out of the salt solution. Hemolysis is complete at 0.32 per cent to 0.36 per cent salt solution, evidenced by the laking of the entire mass of corpuscles suspended in the salt solution so that there is no residue when the tube is briskly shaken. The fluid is stained an even red by the free hemolysis and should be clear and transparent. Fragility is increased in jaundice of the hemolytic type, either of the acquired or of the congenital variety, that is, hemolysis begins in hypotonic solution as strong as 0.48 per cent or 0.5 per cent. The cells are completely broken up at 0.40 per cent or 0.42 per cent sodium chlorid solution. When the cells of tubes con-



taining blood of a person suffering from this malady are compared with those of a normal person's blood, there is a striking difference in the point of beginning and complete hemolysis. On the other hand, in pernicious anemia as in the obstructive type of jaundice, either the erythrocytes are normal in their relation to hypotonic salt solution, or there may be an increase in resistance rather than an increase in fragility, so that hemolysis may not begin except at the low point of 0.36 per cent or 0.34 per cent and it may be complete in only 0.28 per cent sodium chlorid solution, or it may even be incomplete at this lowest dilution so that there is some corpuscle residue even in the very low strength solutions. While this test is not by any means necessary in the ordinary typical case of pernicious anemia, it has been found on several occasions to have been of value in differentiation when there was some question as to whether we were dealing with pernicious anemia or hemolytic jaundice. A definite diagnosis of hemolytic icterus is of importance, as splenectomy usually results in the cure of the condition.

Eppinger's work in the estimation of urobilin and urobilinogen in the stool stimulated interest in this manner of estimating blood destruction, especially in cases of pernicious anemia and hemolytic jaundice. He made use of the Charnas spectrophotometric method which is somewhat complicated for the ordinary clinical laboratory. In this country the more simple procedure for making a quantitative estimation of these substances was devised by Wilbur and Addis. Recently we<sup>3</sup> have used a still further modification originated by Schneider, and have reported our results in a large series of cases. Schneider's test depends on the adaptation of the Wilbur and Addis method for determining the quantity of urobilin and urobilinogen in the duodenal contents recovered by means of the Einhorn or Rehfus tube. There is very little technical difficulty in obtaining a sufficient quantity of fluid from the duodenum by this method. The only precaution necessary is to be certain to exclude anything but fluid coming directly from the duodenum, that is, gastric contents should be siphoned out first. Then as the capsule moves from the pylorus into the duodenum the fluid becomes yellow in color and finally a clear bile is obtained. It may vary in color from pure yellow to a chocolate brown. The fluid should be tested by means of litmus or Congo-red and nothing but alkaline fluid should be kept. The duodenal contents should be collected in a small amber colored bottle and as rapidly as possible about 20 c.c. of

the liquid should be collected. This 20 c.c. portion is divided in two 10 c.c. portions in two 25 c.c. graduates. One portion is used for a rough quantitative estimate of the amount of bilirubin present in the bile. To the other portion are added exactly 10 c.c. of an alcoholic solution of zinc-acetate, so-called Schlesinger's reagent. The mouth of the graduate is closed with the thumb and the contents thoroughly shaken for about one minute. The mixture is then filtered through a single layer of coarse filter paper, 10 c.c. of filtrate being collected in another clean graduate. This filtrate now contains 5 c.c. of duodenal contents and 5 c.c. of Schlesinger's solution. To it is added exactly 1 c.c. of Ehrlich's aldehyde reagent with a 1 c.c. pipette. If urobilinogen is present in any considerable amount, the fluid is apt to turn slightly red on the addition of the Ehrlich's reagent. If urobilin is the chief constituent present, there is a green opalescence in the fluid when viewed by reflected light. The mixture is set in the dark for about fifteen minutes before it is examined with a spectroscope. This length of time seems necessary to sharpen the absorption-bands of the spectrum. With the ordinary type of spectroscope it is not difficult to detect the absorption-bands due to these substances. Urobilin presents a broad band at the blue end of the spectrum. The violet rays are completely absorbed. Urobilinogen absorbs a narrow portion of the spectrum at the yellow edge of the green, and if present in large amounts the band may be large enough to obliterate the entire yellow portion of the spectrum. The method of ascertaining the quantity of these substances present follows the system of Wilbur and Addis, which depends on the number of dilutions necessary for the disappearance of the absorption-bands from the spectrum. The Wilbur and Addis method also reckons the number of units in 1000 c.c. of fluid. As the examination is made on only 5 c.c. of the original solution the factor 200 is necessary to give the findings for 1000 c.c. The number of dilutions necessary for extinction is multiplied by 200 to find the total number of units in 1000 c.c. The total number of units is the sum of the units of urobilinogen and urobilin. In pernicious anemia and hemolytic jaundice the total reading is more than 1000 units—often 3000 or 4000—while in secondary anemia there are only a few hundred units or even only a trace. Though this method may seem intricate to some and though it may be criticized by others as being very crude in its quantitative value, a number of observations that we have made has convinced us that it is not without worth in adding to our knowledge

in those diseases marked by blood destruction. It will not aid in differentiating severe hemolytic jaundice and pernicious anemia as in both of these conditions we have blood destruction and high values for urobilin and urobilinogen, although it is true that mild hemolytic jaundice usually gives comparatively much higher values than does pernicious anemia. In a group of miscellaneous cases it was found, however, that unusually low values were obtained for secondary anemias, carcinoma, tuberculous peritonitis, syphilis, chronic infectious arthritis, gallstones, and myelocytic leukemia. The values were especially low in cases of hemorrhage. Recently Schneider has reported on the subject of aplastic anemia. In these cases he made use of his method in ascertaining in the duodenal fluid the amount of urobilin and urobilinogen, the first time this particular test of blood destruction has been applied to this disease. He found that contrary to the findings in pernicious anemia with low erythrocyte count there was not a high value for these two bile derived pigments. These are the findings of a non-hemolytic anemia. He is inclined to emphasize the fact that a study of the pigments is advisable for differential diagnosis of the aplastic from the hemolytic types of anemia and to consider this disease as an atypical form of progressive pernicious anemia.

A severe anemia of unexplained origin is an indication for serologic tests for the exclusion of syphilis. I think it is safe to say that a large proportion of the persons with profound anemia who appear at our clinic have one or more Wassermann tests as a matter of routine examination. If the Wassermann test is strongly positive, syphilis is at once suspected as a cause for the blood picture. The syphilographer and the clinician agree that there is a very severe anemia simulating pernicious anemia due to syphilis. The anemia may respond at once to antisypilitic treatment but it is not probable that this improvement is due merely to the arsenic used intravenously. Ordinary types of pernicious anemia do not respond so readily to this form of arsenic treatment. Typical pernicious anemia with syphilis is rare, so rare that it may be coincidental. Naturally the objection is raised that we are not dealing with pernicious anemia if we have a severe anemia in syphilis, no matter what the blood picture. It is also of interest, however, that many of these patients do not respond to antisypilitic treatment until they are first treated for severe anemia and it is remarkable that they begin to respond to treatment with arsphenamine or other intravenous treatment only if their blood

condition has been improved by transfusion or other means employed in the treatment of pernicious anemia. We have also seen patients with persistent total inhibition Wassermanns who have all the findings of pernicious anemia who have not been benefited by any form of treatment. These patients die with all the symptoms of pernicious anemia. This fact has raised in my mind a question that should be considered from a serologist's standpoint, whether progressive pernicious anemia in itself may not occasionally bring about changes in the serum of the person that produce a non-specific fixation of complement with the ordinary Wassermann technic. The obvious answer to this question is that the great majority of cases of pernicious anemia are Wassermann negative. However, all serologists realize that our knowledge of the phenomenon of complement fixation is exceedingly meager and that even in syphilis itself the reaction cannot be considered truly specific.

Two intestinal parasites, the fish tapeworm, *Bothriocephalus latus*, and the hook-worm, are reported in the literature as causing symptoms of pernicious anemia. A profound anemia would suggest to the clinician the examination of the patient's stool as a necessary laboratory examination. In the South where hook-worm infections are prevalent, such an examination often reveals the cause of the severe anemia, and the proper treatment brings about a cure. Such a disease is, of course, thus classed as uncinariasis and not classical, progressive pernicious anemia. In the Mayo Clinic, hook-worm infections play little part in the diagnosis of the anemias, as we see few patients of this type from the southern states. Those that we have seen have been cases of a more or less mild type, without the pernicious anemia blood picture. The same may be said of the much rarer infection with the fish tapeworm. I believe it is true in nearly all clinics in this country that *Bothriocephalus latus* infections may very readily be excluded by the history and by a stool examination.

In the examination of the stools in the routine manner of persons with severe anemia and with all the symptoms of pernicious anemia, some form of intestinal parasite is often found. It is not unusual to find such a person infected with some of the common protozoa of the flagellate group or even amebæ of the pathogenic type, *Endamæba histolytica*. If there is diarrhea and amebiasis, the diagnosis may be somewhat complicated by this finding. The question arises whether the parasites are commensal invaders of the alimentary tract of a

person whose resistance is low, owing to the blood disease, or whether the infection is so severe that the intestinal symptoms are due to the parasites, and the anemia, though of the primary type, is truly secondary to the intestinal infection. The treatment of true pernicious anemia patients for amebiasis has not been attended with marked success. While the patient may have the parasites removed from the intestinal tract to such an extent that all subsequent stool examinations are negative, other measures are necessary to improve the blood condition.

Another protozoal parasite which I believe must be considered somewhat in detail is *Balantidium coli*. This organism is easily recognized when once seen in the stool. It is larger than the ameba. Its rapid motion by means of the cilia that completely cover the ectoplasm of the organism at once attracts the attention of the microscopist. The peculiar morphology of the large parasite, the peristome lined with stout cilia, the macronucleus and the micronucleus are all readily pointed out. Severe symptoms of a chronic intestinal nature are attributed to this organism so that in the tropics fatal cases of this type of infection are not uncommon. This parasite as a cause of disease in this country is rare but a number of cases have been observed in various parts of the country. We have seen a small number of persons infected with this parasite who have had a blood picture of pernicious anemia. I believe this point has not been greatly emphasized in the literature and I feel that it is one that merits some attention in the study of the anemias.

There is one point in the physical diagnosis connected with severe anemias that should be emphasized in the discussion of special diagnostic methods; that is, the inspection of the mouth for foci of infection, at the same time paying special attention to the tongue. To be sure, this should be a part of any ordinary physical examination; however, it must not be forgotten that the tongue in cases of pernicious anemia presents a peculiar glossitis that in itself may make the examiner suspect that he is dealing with something more than the ordinary type of secondary anemia. The patient may or may not complain of soreness of the tongue although often a severe glossitis may be a part of the clinical picture. The absence of the papillæ of the tongue is so striking that the expression "bald" tongue is used as typically descriptive of this particular condition. In a large proportion of the advanced cases of pernicious anemia that we see, this condition has been noted in the history as one of the striking points in the physical examination.

In this discussion of the anemias, I have said very little that can be applied to any disease except pernicious anemia or as it is distinguished from those conditions that resemble pernicious anemia. The pathology and physiology involved in the discussion of the anemias calls for a longer discussion than would be suitable at this time. I have not placed much emphasis on the diseases that have been known to be benefited by surgery. Splenic anemia in the child or young adult evidenced by a blood picture of secondary anemia, leukopenia, a large spleen and hemorrhage from the stomach, presents very little in its history or blood findings that confuses it in any way with pernicious anemia. It must, however, be distinguished from syphilis, chronic recurring sepsis, or malaria with splenomegaly. The pseudo-leukemia of infants or von Jaksch's disease also may be a manifestation of this same condition, although there is a leukocytosis instead of a leukopenia. The fact that splenic anemia is curable by surgery makes it of interest in this symposium. The peculiar color, and secondary type of anemia that is due to myxedema should be mentioned. The recent work of Plummer in establishing the value of the findings of low basal metabolic rate in hypothyroid persons will doubtless prove to be of far reaching importance.

I might also mention one other type of splenomegaly which is very rare and which is easily separated from the pernicious anemia type of anemia. I refer to the so-called Gaucher's disease, in which there is a large-cell splenomegaly with secondary anemia. Clinically, it is difficult to diagnose this disease from splenic anemia, the differentiation being made chiefly on pathologic findings.

In conclusion, then, the clinical laboratories and specialists may add corroborative evidence to the physical findings not only by the microscopic study of the blood, but also by means of the somewhat more elaborate procedures, such as tests for evidence of blood destruction, the resistance of the erythrocytes, the serologic findings as regards syphilis, the analysis of the stomach contents, the examination of the stools for parasites, and the expert examination of the eye grounds and of the nervous system.

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## THE RESULTS OF SPLENECTOMY IN THE ANEMIAS\*

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Splenectomy as a curative agent has been given a fair trial in three types of the anemias, and its successes and failures may be reasonably shown by the data at hand. It is my purpose to discuss the operation in cases of splenic anemia, pernicious anemia, and hemolytic icterus from this standpoint.

### SPLENIC ANEMIA

While splenic anemia is, as pointed out by Osler, a clinical entity, it cannot be said to have a definite pathologic existence. It may be defined as a splenomegalia with a secondary type of anemia which is progressive but not constant until the later stages. This secondary anemia has no special characteristics except that as a rule it is accompanied by a leukopenia, although we have seen otherwise typical cases in adults with leukocyte counts around from 10,000 to 12,000. Splenic leukemia, and it is believed by some clinicians of the present day that von Jaksch's disease (infantile pseudoleukemia) is an infantile form of splenic anemia in which a moderate leukocytosis due to the higher values of leukocytes in the normal blood of infants is to be found.

A number of pathologic conditions of the spleen which more or less resemble splenic anemia have been classified as splenic anemia, especially that of syphilitic splenomegalia. A few clinicians regard all splenic anemias as syphilitic in origin, but this theory is not borne out by our experience. Chronic enlargements of the spleen that are accompanied by anemia and are the result of various protozoa, as in syphilis, malaria and kala-azar, as well as those anemias due to bacteria, typhoid and tuberculosis, were removed from the splenic anemia group when their etiology was discovered.

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Hemolytic icterus has often been confused with splenic anemia. Occasionally pernicious anemia, when accompanied by a large spleen, has been diagnosed splenic anemia. Put in the form of an Hibernianism, incomplete knowledge is essential to the diagnosis. If we know the cause of splenic anemia it is not splenic anemia. It is a question, however, whether we have not been too insistent on the lack of knowledge as evidenced by unknown etiology as one of the chief features of splenic anemia. I believe we would get a much better idea of splenic anemia if we made the pathologic condition of the spleen and its effect on the blood the criteria, and classified as splenic anemia all cases of known causation as well as those of unknown causation, assuming that in the course of time we shall find the toxic agents which produce the condition of the spleen.

The pathologic characteristics of the spleen in splenic anemia are generalized fibrosis with compression atrophy of the malpighian corpuscles, and endophlebitis. It may be said that enlarged spleens that show such characteristics will develop chronic anemia without regard to causation. In five instances we removed large spleens in cases of chronic intractable syphilis with severe anemia in which the patients had been carefully treated for syphilis for months. After the removal of the spleen, the anemia rapidly disappeared and the syphilis was cured with comparatively mild antiluetic treatment, such as had previously failed to affect either the syphilitic condition or the spleen. In 3 of these cases gummas were found in the liver, in 2, small gummas were found in the spleen, and in 2 the spirochete was stained in the splenic tissues.

In 1883 Banti first described an enlargement of the spleen accompanied by atrophic cirrhosis of the liver of the Laennec type. The relation of splenic anemia to Banti's syndrome is most interesting. The majority of clinicians, I believe, agree with Moschcowitz in the conclusion that there is no real difference between the two and that Banti's disease is merely a late phase of some cases of splenic anemia. It is certainly true that a considerable percentage of cases of splenic anemia in the later stages will be found to be associated with portal cirrhosis of the liver but not always of the atrophic type; the liver is as frequently enlarged as contracted. On the other hand, some observers believe that all cases of this description are primarily portal cirrhosis and that the splenomegalia is secondary. When the condition is seen in the later stages, it is difficult, if not impossible, to determine whether

it was primarily portal cirrhosis with secondary splenic manifestations, or primarily splenic anemia.

Gastro-intestinal hemorrhages, especially hematemesis, and ascites occur in splenic anemia and in portal cirrhosis. After all, cirrhosis of the liver is essentially a fibrosis which exhibits more fixed characteristics than the spleen because the liver cells are all of one type and react uniformly to chronic irritation, while the spleen has differentiated groups of cells which permit of wide architectural changes. It is also to be noted that the blood comes directly in contact with the splenic pulp, as the vessels retain only their endothelial coverings; this may account for the endophlebitis, which is so marked a characteristic of splenic anemia. Occasionally an enlarged spleen will be found, especially in women, without known cause and without anemia. This condition may exist for years, but eventually anemia results. In several cases of this type, when the patients finally came to operation, the spleen was fibrotic. It is probable that fibrosis of the spleen from any cause will eventually produce chronic anemia and, other things being equal, such spleens should be removed when appropriate treatment fails to cure.

Of 61 patients with splenic anemia from whom we removed the spleen 7 (11.7 per cent) died.\* The deaths occurred in patients operated on in a late stage of the disease, in which there was a high grade of anemia, ascites, and cardiorenal manifestations. In three patients acute thrombosis of the superior mesenteric and portal veins was the immediate cause of death; extensive thrombosis, evidently of long standing, was found in the splenic veins. These observations are in accord with those of Dock and Warthin, who found extensive thrombosis of the splenic vein in 2 patients who died from splenic anemia and in which there was ascites without cirrhosis of the liver. It would appear that the spleen, acting as a filter, removes noxious agents, both microorganisms and chemical toxins, from the blood stream and sends them to the liver for destruction; in certain instances cirrhosis of the liver as well as fibrosis of the spleen results from the chronic irritation produced by such substances. If the spleen is unable to rid itself of all these toxic agents, splenomegalia and anemia result with sequestration of the agents in the spleen, as in spirochetal

\* These statistics extend to Dec. 31, 1918, and include as operative deaths all patients dying in the hospital without regard to cause of death or length of time after operation.

and plasmodial infections, but the liver is not necessarily cirrhotic. Why the liver is cirrhotic in some cases and not in others is not known.

Both portal cirrhosis and splenic anemia lead to death through portal obstructions, and the hemorrhages and ascites are due to back pressure. If the spleen is removed early in splenic anemia, we know by experience that the liver will probably not show serious evidences of disease later, and even when cirrhosis of the liver is well marked and ascites is present, removal of the spleen often effects a "near" cure. The first thought is that by removing the spleen toxins filtered from the blood are prevented from passing to the liver. On further consideration it seems that the true explanation is this: Inasmuch as the normal spleen carries about 30 per cent of the blood to the liver and that from these huge spleens the splenic vein may carry as much blood to the liver as the remaining elements of the portal vein, splenectomy relieves the liver of its overload and reduces its labor sufficiently to enable it to meet its demands, just as sometimes follows the Talma-Morison-Drummond operation. Fagge, many years ago, described a series of cases in which persons apparently in perfect health, coming to death by accident, proved at necropsy to have advanced cirrhosis of the liver, but with so good a compensatory circulation along the vascular channels of Sappey as greatly to reduce the circulation in the liver and enable it to maintain its function.

Many patients splenectomized in the late stages of the disease with marked ascites, frequent hemorrhages from the stomach, and so forth, have been cured. Balfour, in a recent article on gastric hemorrhages of splenic origin, reports in detail a case in which the removal of a spleen a little larger than normal checked gastric hemorrhages of many years' duration, from which the patient was almost exsanguinated. The patient has remained well for nearly three years. We have since had a similar experience. A patient in extremis for whom repeated blood transfusions failed to afford even temporary relief was cured by splenectomy. Sherren and others have called attention to the fact that after the removal of the spleen for splenic anemia an occasional patient has a recurrence of hemorrhages. We have had one case of this kind, but such experiences are unusual. I would call attention to the important fact that in 5 of these cases the diagnosis of splenic anemia was not definitely established, but the 5 cases fitted into this group better than into any other. Future progress in knowledge of splenic conditions may change the interpretation of the facts and alter the diagnosis.

## PERNICIOUS ANEMIA

The etiology of pernicious anemia is unknown, the early symptoms are indefinite, and by the time the diagnosis can be made the disease is incurable. The disease may be described as a progressive degeneration of the red blood in which there is a loss of the blast or mother cells of the erythrocytes; the blast cell when lost is not replaced. In contrast to splenic anemia which is of the secondary type, the blood picture in pernicious anemia has characteristic cells which mark the disease. The color index, or hemoglobin percentage, is higher in proportion to the number of red cells present than in the secondary anemias. The lemon color of the skin, sometimes with an icteroid hue, is so different from that in the secondary anemia that sometimes a diagnosis is possible by looking at the patient. This icteroid hue is more prominent in cases in which hemolysis is marked, as shown by examination of the duodenal content after the Schneider method. If we might assert that in cases of pernicious anemia in which hemolysis is most marked patients have a greatly enlarged spleen or that the spleen exhibits definite pathologic changes, we would have succeeded in establishing a direct connection between the enlarged spleen so often found and the disease. Unfortunately, our experience does not support this hypothesis, and the size of the spleen does not seem to bear a definite relationship to the severity of the disease. Necropsy, after death from pernicious anemia, as a rule shows a small spleen, but in 2 only of our cases was the spleen below normal (195 gm., Sappey) at operation, and both were terminal cases.

The average weight of the spleens removed in our cases of pernicious anemia was 400 gm., exclusive of two large spleens, one of which weighed 2220 gm. and the other 1600 gm. It seems probable, therefore, that in pernicious anemia the spleen is enlarged during the early and middle stages, and that the contraction so often found at necropsy is a terminal condition. The question is as yet unanswered whether pernicious anemia is a definite and specific entity, or whether it is a terminal change of several conditions, and recognized only as pernicious anemia when the patient has reached a stage which we know will eventually cause death.

Any form of treatment for pernicious anemia may prove, or at least may appear to be, beneficial. Even without treatment these patients have their ups and downs, and it is not an infrequent clinical experience

to have a patient present himself with symptoms which might be construed as being those of an early pernicious anemia, and then with or without treatment recover and remain well. In eliciting the history the physician finds that the symptoms are often indefinite in the earlier stages, before the blood changes become characteristic.

Splenectomy in pernicious anemia does not appear to be based on sound reasoning and there seems to be no foundation for the belief that the procedure will cure pernicious anemia. Eppinger first suggested splenectomy as a cure for pernicious anemia, and the early reports with the abundant testimony as to temporary relief were quite sufficient to give the operation a fair trial in this hopeless disease. Considering the confusion which so often attends the early diagnosis, it seems probable that obscure cases of hemolytic icterus and splenic anemia have been accidentally included in the pernicious anemia group. Removal of the spleen in such cases has given the impression that splenectomy cures pernicious anemia. At the same time in the investigation of our cases of splenectomy for pernicious anemia, we see great, though temporary, improvement. There is a gain in weight and an improvement in the blood from an average hemoglobin of 38 to 72 per cent, and the reds from two to four millions. Splenectomy seems at least to have instituted a marked palliation.

In our experience in the cases in which the results were most favorable the symptoms were less characteristic of pernicious anemia. In young and middle aged persons in whom the disease is most rapid, especially if hemolysis is known to be marked, splenectomy is worthy of trial. Taken as a whole, it may be said that whenever pernicious anemia has developed to the stage in which the blood is characteristic it is incurable, and splenectomy is a means of palliation and not of cure. Since there is an operative mortality good reasons must exist for substituting operation for repeated blood transfusions. We have splenectomized 50 patients with pernicious anemia with three deaths (6 per cent).

#### HEMOLYTIC ICTERUS

Hemolytic icterus has not been classified with the anemias, but as pointed out by Kanavel and Elliot, the peculiar splenic activity results in an anemia which is the cause of death. As in splenic and pernicious anemias, the etiology of hemolytic icterus is unknown. The well developed hemolytic icterus stands out with a vividness, unequaled

in splenic anemia and in pernicious anemia. These three diseases, all of unknown etiology and lacking sound pathologic foundation, when examined in the minutiae are without distinctive features. Viewed in the perspective they are outstanding clinical entities. The characteristic features of hemolytic icterus are an enlarged spleen, chronic jaundice with exacerbations, normally bile colored feces, and absence of bile in the urine.

It is certain that in hemolytic icterus the spleen destroys, unnecessarily, the red corpuscles; the enlargement of the spleen may be in the nature of a work hypertrophy. Enlargement of the liver is usually present and may also be a work hypertrophy. In some of our cases sections from the liver showed definite hyperplasia of liver cells.

There are two types of hemolytic icterus, the familial or congenital type of Minkowski, and the acquired type of Hayem and Widal. In the familial type the disease may be noticed from infancy and it may not be progressive; the patients live the allotted span of years in a fair degree of health, but with more or less jaundice throughout life. These cases are not uncommon and are to be seen in every community; in a large percentage a more serious condition develops which makes them indistinguishable from the acquired type, and as in the acquired type, the disease progresses in the course of some years to a fatal ending.

Chauffard and Widal have pointed out that the red cells are less resistant in hemolytic icterus than normally, and our experience confirms these observations. Sanford has worked out a simple and very reliable method of examination for red cell fragility which we have used in the clinic extensively and with great satisfaction.

#### THE RELATION OF HEMOLYTIC ICTERUS TO THE LIVER AND ITS CIRRHOSSES

We find in hemolytic icterus an occasional case in which biliary cirrhosis is associated. Brushing aside the familiar classification of the cirrhoses of the liver in which variations in the morphology lead to unnecessary confusion, there are but two fundamental hepatic cirrhoses: (1) The portal, in which the toxic material reaches the liver by way of the portal vein, and in which the connective tissue is deposited about its radicals and death is caused by portal circulatory obstructions, ascites, and gastro-intestinal hemorrhages without jaundice until

shortly before death, and (2) biliary cirrhosis, caused by an infection of the biliary ducts in which the connective tissue is deposited about the biliary ducts, causing jaundice but without ascites or hemorrhages until shortly before death. More often this is an ascending infection from associated gallstone disease, especially gall stones in the common duct; at times it is hematogenous from focal infections in any part of the body; the pancreas is frequently associated in a chronic pancreatitis. Just as we have many varieties and subvarieties of portal cirrhosis, so we have many varieties and subvarieties of biliary cirrhosis, but we should not be led astray by the many patterns which may appear any more than we should name wall-papers or carpets differently according to their patterns. Normally blood pigments are the source of the coloring matter in the bile. In hemolytic icterus the enormous destruction of red corpuscles in the spleen inundates the liver with blood pigments, and renders the bile thick. One can conceive that, under such circumstances, a liver which has a superabundance of work of a certain kind thrown upon it may deposit pigments throughout its tissue, thus producing many of the patterns which are given as varieties of biliary cirrhosis. As there is no infection there is no cirrhosis, but there is, as I have stated, some enlargement of the liver.

The viscid bile in hemolytic icterus tends to form gallstones. Sixty per cent of all the patients with hemolytic icterus on whom we operated had associated gallstones and all the possibilities of biliary duct infection. It may readily be understood why biliary cirrhosis is sometimes associated with hemolytic icterus and why the two diseases have been confused. It should not be forgotten that in portal cirrhosis and in biliary cirrhosis the entire liver may not be involved in the cirrhosis. We frequently see limited areas of cirrhosis without attending symptoms because the organ is not extensively involved. Hemolytic icterus has been most often confused with the elusive syndrome termed Hanot's cirrhosis, which, so far as I know, has no pathologic foundation, and if it occurs clinically I have never seen it.

The triumph of splenectomy is the cure of hemolytic icterus. We have had no more satisfactory results in surgery than are to be found in this group of cases. Only patients in a terminal condition with secondary gallstones and cirrhosis of the liver fail to be relieved. The only patient we lost of the 27 splenectomized for hemolytic icterus was one operated on during an acute exacerbation. Crises are a part of the

picture of the disease, and when severe have usually been due to gallstones, although it is undoubtedly true that exacerbations do take place from unknown causes in which there is great but temporary increase of jaundice, with tenderness and increased tumefaction of the spleen and usually of the liver, without gallstones. On gross section the spleen in hemolytic icterus is dark, mottled, filled with blood pigments, and quite distinct from the spleens which we have removed for other conditions.

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## PERSISTENT EOSINOPHILIA WITH HYPERLEUKOCYTOSIS AND SPLENOMEGALY\*

H. Z. GIFFIN

As the basis for a discussion of eosinophilia I wish to review a case which seems to be unique in medical literature: eosinophilic hyperleukocytosis associated with marked splenomegaly and moderate glandular enlargement. This case suggests a consideration of (1) the origin and function of the eosinophils, (2) the clinical incidence of eosinophilia, (3) the occurrence of eosinophilia with hyperleukocytosis, and (4) the possibility of the existence of an actual eosinophilic leukemia, apparently following splenectomy in a case of eosinophilic hyperleukocytosis.

CASE 81201. F. H., male, aged thirty-one years. Marked splenomegaly. Slight enlargement of superficial lymphatic glands. Leukocytosis 21,800 before splenectomy, with an eosinophilia of 73.6 per cent. Splenectomy July 15, 1914. Weight of spleen 2110 gm. Macroscopic appearance of spleen similar to that in myelogenous leukemia. Rapid increase of leukocyte count to 97,200 and later to 211,000, eosinophilia from 79 to 90.7 per cent. Good general condition for period of four years following splenectomy. Death Jan. 19, 1919, of empyema following pneumonia. Necropsy: Enormous numbers of eosinophilic polymorphonuclears in all hemopoietic organs. Eosinophilic myelocytes numerous in lymph glands, spleen and bone-marrow. Obliterative pericarditis and fibrous perihepatitis.

March 11, 1913, a man, aged thirty-one years, with generalized anasarca and moderate anemia, presented himself for examination. His family history was negative. He had had a continuous fever, with the characteristics of typhoid fever, eight years previously, and this had been followed by pneumonia. Convalescence from this severe illness was protracted and the patient had not since that time entirely regained his former strength. Eighteen months before the examination he developed moderate dyspnea and a cough; he had an occasional attack of vomiting and some wheezing, but did not have a typical paroxysmal asthma. Thirteen months before, he had

\* Presented before the Association of American Physicians, Atlantic City, June, 1919. Reprinted from *Am. Jour. Med. Sc.*, 1919, clviii, 618-629. Copyright, 1919, by Lee and Febiger.

been much annoyed by a severe recurrent pain in the left thoracic region; this, in the light of later findings, may have been due either to a pericarditis, a pleurisy or to a perisplenitis. Ten months before examination a transitory edema of the legs and face developed, which would disappear during the night. Five weeks previous to examination the patient became quite ill with cough, shortness of breath and wheezing, without chill or fever. He could not work, but was not confined to bed. Three weeks before examination he began to suffer from a moderately severe pain at the right costal margin, associated with vomiting and questionable jaundice. One week before examination a generalized edema developed and became progressively worse.

The general physical examination showed a marked superficial edema of the legs and body up to the level of the arm-pits. The scrotum was edematous; evidence of ascites was present, the liver and spleen were enlarged and the axillary glands were easily palpable. There was no definite evidence of lues and the Wassermann test was negative. There was no indication of nephritis. The acute condition at that time seemed to be due either to a myocardial insufficiency or a cirrhosis of the liver.

The most interesting finding, however, was the presence of eosinophilia of 66.3 per cent (Table 1). The leukocyte count at the time

TABLE 1.—BLOOD COUNTS (CASE 81201, F. H.)

Date .....	March 11, 1913	Dec. 16, 1913	July 14, 1914	Aug. 5, 1914	Nov. 24, 1914	May 25, 1915	Dec. 5, 1916	May 15, 1917	Oct. 10, 1917	Nov. 26, 1918
Hemoglobin...	69	80	75	68	85	70	69	52	58	50
Red blood cells (millions)...	3.62	4.16	3.86	4.02	4.60	3.56	4.25	3.48	3.62	2.72
White blood cells.....	15,400	15,400	21,800	97,200	133,000	208,000	103,000	211,000	135,000	81,800
Small lympho- cytes.....	18.3	16.0	9.6	6.8	11.3	5.0	9.0	3.7	5.3	5.0
Large lympho- cytes.....	1.0	4.8	6.0	1.2	1.3	4.2	0.3	1.0	2.0	1.7
Polymorpho- nuclears....	13.0	19.4	9.8	12.4	10.0	6.8	6.7	4.3	5.7	7.0
Eosinophils...	66.3	57.6	73.6	79.0	75.0	83.4	83.0	90.7	87.0	84.0
Basophils...	1.3	2.2	1.0	0.6	2.3	0.4	...	0.3	...	0.7
Neutrophilic myelocytes...	...	...	...	...	...	...	0.3	...	...	...
Eosinophilic myelocytes...	...	...	...	...	...	0.2	...	...	...	0.7
Normoblasts...	...	...	...	...	...	1.0	1.0	...	...	1.0

of the first examination in March, 1913, was 15,400; the total lymphocyte count was 19.3 per cent, while the polymorphonuclear count was only 13 per cent. The anemia itself was of a secondary type, with a red cell count of 3,620,000 and a hemoglobin of 69 per cent. On account of the extremely high eosinophilia a very careful search for parasites was made. The stools were repeatedly negative and a microscopic examination of skeletal muscle was negative.

A lymph gland removed from the axilla for microscopic examination showed a moderate inflammatory reaction. The germ centers were intact; a marked endothelial hyperplasia was present. Eosinophilic polymorphonuclear leukocytes were quite numerous and a few scattered eosinophilic myelocytes were to be found.

The patient was placed at absolute rest in bed on a milk diet; his edema practically disappeared within ten days. The spleen was then easily outlined and was found to extend to the navel and to the level of the left iliac spine. Two months later the patient was able to do light work. During the summer and fall of 1913 he worked moderately hard and quite regularly. In June, 1914, more than one year after the original examination, the patient's general condition was fairly good. His anemia, however, was quite definite; the red cell count was 3,500,000, the eosinophile percentage was 75.4., while the total leukocyte count was 13,800.

In view of the persistence of a chronic anemia of the secondary type and the presence of a marked splenomegaly, splenectomy was decided on. The operation was performed July 15, 1914, by W. J. Mayo. The spleen was very large, measuring approximately 10 inches by 12 inches, and weighing 2110 gm. Extensive perisplenitis was present and the organ was almost completely adherent to the vault of the diaphragm, to the wall of the stomach, and to the parietal peritoneum. Macroscopically it had the appearance of the spleen in myeloid leukemia. The liver, especially the left lobe, was very large. A small amount of abdominal fluid was present. The gall-bladder was distended, but gallstones were not palpable.

Splenectomy was followed by a gradual and steady improvement, especially with respect to the patient's strength and general condition. Within one month after splenectomy, however, the leukocytes had risen from 21,800 to 97,200, 79 per cent of which were eosinophils. During the fall of 1914 the patient felt better than for seven or eight years. His weight was 159 pounds and he was able to do light work.

The liver remained enlarged and in November, 1914, it extended three finger-breadths below the costal margin. The superficial glands in the neck and axilla were easily palpable. During 1915 the patient's general condition was quite satisfactory, aside from slight shortness of breath on exertion. During the winter of 1916 there was a slight increase in the size of the liver and a superficial edema was occasionally present, but by summer the patient was so improved that he was able to do regular farm work. A pruritus of indeterminate type developed; this may have been an expression of the patient's chronic toxemia. In 1917 the patient's general condition was quite satisfactory except for occasional attacks of pruritus and of moderate dyspnea and edema. Oct. 10, 1917, the leukocytes numbered 135,000, 87 per cent of which were eosinophils. The patient continued to be in fairly good health until October, 1918, at which time a gradually increasing weakness, dyspnea, and cough developed, later associated with an acute illness, which probably was pneumonia, as our examination in November, 1918, revealed evidences of unresolved pneumonia, and a roentgen-ray examination of the chest showed an infiltration in the region of the right middle lobe, together with a considerable enlargement of the cardiac shadow. The patient was anemic, the hemoglobin being 50 per cent and the red cells 2,720,000. The patient was advised to have hospital care and observation, but this was refused; one month later he returned in a very bad condition. There was then evidence of fluid in the right pleural cavity. A catheter was inserted through a cannula and 1300 c.c. of yellow pus were aspirated. A culture showed pneumococci. Through an oversight a cellular and chemical study of the pus was not made. The pleural cavity was treated with Dakin's solution. The patient's general condition was not satisfactory after the development of empyema, and Jan. 18, 1919, his temperature rose rather suddenly to 102°; he died Jan. 19, 1919, probably as the direct result of bronchopneumonia.

*Cytology of blood smears.*—A study of the blood smears revealed that almost all the eosinophils were of mature type and differed only slightly from the eosinophilic polymorphonuclears which are ordinarily found in the blood stream. These cells were somewhat larger than usual and the number of nuclear lobes was increased. Many cells had three lobes. The protoplasm seemed to be basophilic rather than neutrophilic and a considerable vacuolation was present and a few cells were ruptured. Certain eosinophils were to be seen in which

a few small basophilic granules were present and an occasional eosinophil had the appearance of a transitional cell or metamyelocyte with a horseshoe nucleus. Rarely, however, was it possible to discover a true eosinophilic myelocyte in the blood smears (Plate I).

*Examination of the spleen removed at operation July 15, 1919.\*—*The spleen, weighing 2110 gm., was approximately 10 by 12 inches.

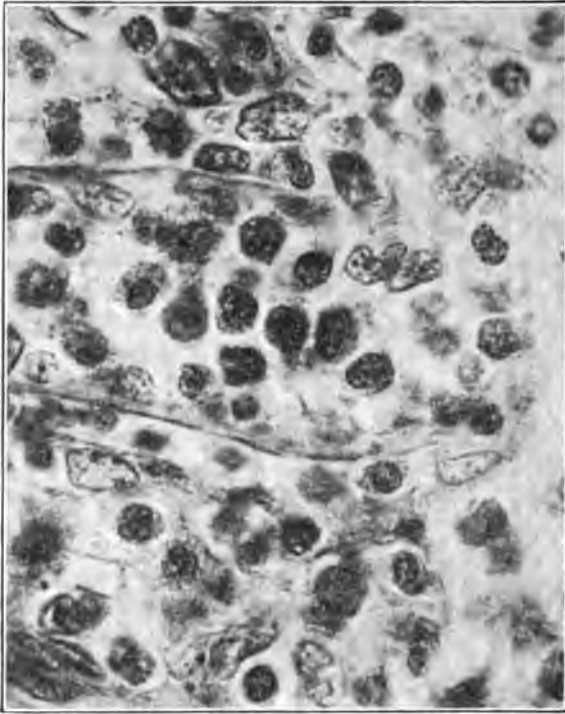
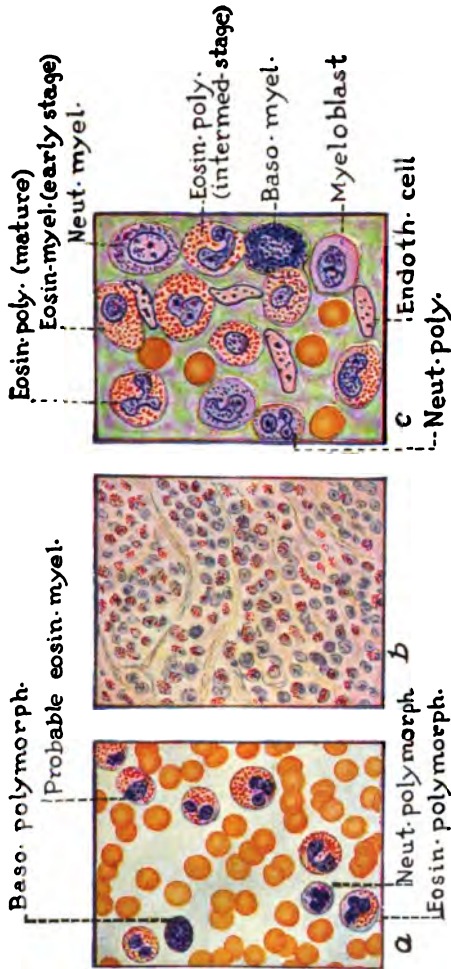


FIG. 250.—Microphotograph of spleen, showing eosinophilic polymorphonuclear leukocytes and myelocytes. They are not so plain in the spleen as they are in the lymph gland (Fig. 253), due to poor fixation.

The malpighian bodies were intact though not numerous. Cellular hyperplasia was marked, eosinophilic polymorphonuclears were very numerous, and a few eosinophilic and neutrophilic myelocytes were seen. The increase in the amount of fibrous tissue was only slight (Plate I). The myelocytes were much less numerous in the spleen, which was removed in 1914, than they were in the glands removed at necropsy four and one-half years later.

\* Examination of tissues was made by A. C. Broders.

# PLATE I



Drawings of actual fields to show eosinophiles: *a*. Eosinophiles in the blood stream, observed with 10 × ocular and ¼ immersion oil objective. *b*. Bone-marrow cells showing remarkable predominance of eosinophilic myelocytes, ¼ objective, 10 × ocular. *c*. Bone-marrow under ¼ immersion oil objective and 10 × ocular.



*Examination of the bone-marrow (Postmortem Jan. 19, 1919).*—The bone-marrow was hyperplastic and contained great numbers of eosinophilic polymorphonuclear leukocytes; the majority of them were in a well-developed stage while a few were apparently of intermediate type. Eosinophilic myelocytes were present in the proportion of 3 to 10 in favor of eosinophilic polymorphonuclears. An occasional neutrophilic polymorphonuclear and, very rarely, a basophilic mye-

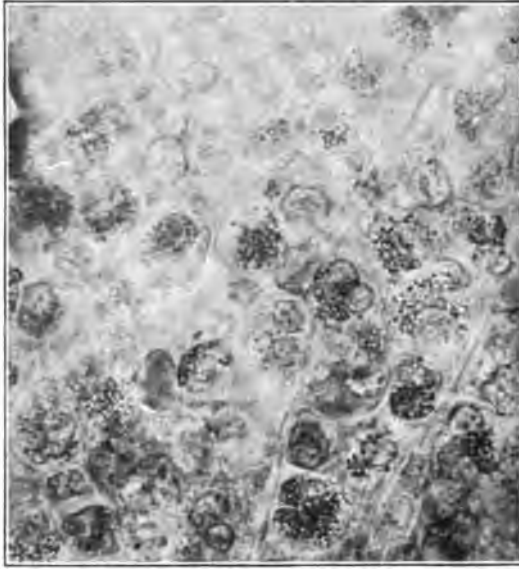


FIG. 251.—Microphotograph of bone-marrow, showing numerous eosinophilic polymorphonuclear leukocytes and a few eosinophilic myelocytes. The coarse granules, often clumped at one side of the cell, are prominent. 10 × ocular, 1/12 objective, Jenner stain.

locyte could be found. The erythrogenic function of the bone-marrow seemed to be almost in complete abeyance (Plate I and Figs. 251 and 252).

*Examination of the lymph gland from the region of the head of the pancreas.*—The gland was about 3 cm. in diameter. The germ centers were intact. Eosinophilic polymorphonuclears were very numerous. A few scattered eosinophilic myelocytes and neutrophilic myelocytes were found. The eosinophilic myelocytes occurred in the proportion of 1 to 10 in favor of the eosinophilic polymor-



phonuclears. The eosinophilic polymorphonuclears showed chiefly fully developed forms and occasionally intermediate forms. The eosinophilic polymorphonuclears were almost as numerous as the lymphocytes (Fig. 253).

*Anatomic diagnosis.*—Right bronchopneumonia; right fibrous pleuritis; obliterative pericarditis; fibrous perihepatitis; cirrhosis

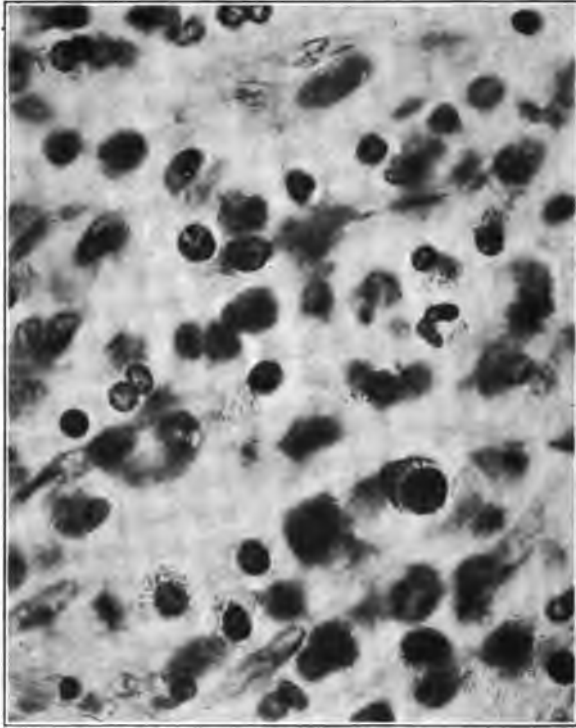


FIG. 252.—Microphotograph of bone-marrow, showing eosinophilic myelocytes and polymorphonuclear leukocytes.

of the liver; general lymphoid hyperplasia. The obliterative pericarditis and the fibrous perihepatitis were probably of long standing and much of the symptomatology during the last six years of the patient's life could be attributed to cardiac and hepatic disease. While these latter pathologic conditions were apparently of a chronic nature the cirrhosis of the liver was of mild grade and of mixed type, but a generalized fibrous peritonitis, commonly seen in Pick's or Concato's disease, was not present.

## DISCUSSION

1. *The origin and function of the eosinophils.*—Most hematologists subscribe to the heteroplasmic theory of the formation of granular cells, at the same time admitting the occurrence of mitosis and the homoplasmic origin of a certain number of these cells. They agree that eosinophilic polymorphonuclear leukocytes develop chiefly from un-

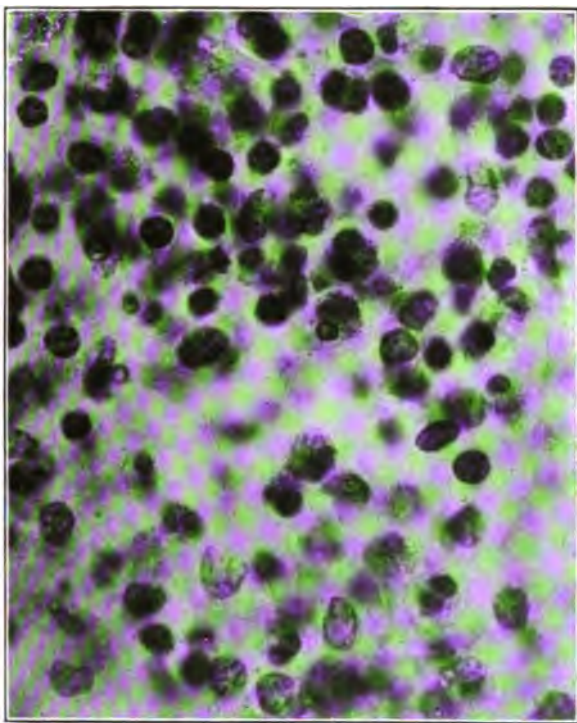


FIG. 253.—Microphotograph of large lymph gland near the head of the pancreas, showing numerous eosinophilic polymorphonuclear leukocytes and a few eosinophilic myelocytes.

differentiated mononuclear cells within the bone-marrow, and in smaller numbers within certain special tissues of the organism, particularly lymphoid tissue. Whether this development is a direct transformation from lymphocytes or is the result of maturation from metastatic bone-marrow tissue is undecided. In the case herewith reported the presence of eosinophilic myelocytes and immature forms of eosinophilic polymorphonuclears in the spleen and lymph glands

indicates quite clearly either a normal or a perverted production of eosinophils within these organs. There is no conclusive evidence in favor of the theory of the direct transformation of neutrophilic polymorphonuclears into eosinophils either in the blood-stream or in the general tissues. The theory of the origin of eosinophilic granules from hemoglobin or its dissociation products is strongly advocated by Weidenreich. The recent work of Downey shows that in the bone-marrow of the adult guinea pig eosinophilic granules are differentiated gradually from a basophilic protoplasm and that their progressive evolution is marked by complex changes in staining reactions, size and shape, and also that there is a direct transformation from basophilic to oxyphilic granules. The complex evolution of the granules indicates that they are true endogenous formations. The granules of eosinophils even in the younger cells and before they become clearly oxyphilic can be differentiated from the granules of mast-cells by their size, shape, and staining characteristics. Downey explains that there need be no conflict between his own conclusions concerning the endogenous origin of eosinophile granules in the bone-marrow and Weidenreich's demonstration of an exogenous origin as a result of phagocytic activity. This can be explained on the basis of Gütig's theory that two types of eosinophils exist and that, morphologically, they are distinguishable.

Very few facts concerning the function of eosinophils are known. Complete withdrawal of food is followed by a decrease of eosinophils in the peripheral circulation. There is a relationship between nutrition and the production and circulation of eosinophils, and disturbances of nutrition affect the multiplication of eosinophils more readily than that of the finely granular leukocytes (Opie). Schwarz believes that there are indications of a very close relationship between eosinophils and intestinal secretion and that possibly these cells may convey a hormone which is important for proper cellular activity in the intestine. Falta and his co-workers call attention to the fact that pilocarpin and pituitrin, substances which raise the tonus of the autonomic nervous system, also produce eosinophilia.

Lepsky concludes that eosinophilia is, in some measure, a reaction of the organism against the penetration of foreign proteins. Weinberg and Séguin, in 1915, confirmed the work of Mesnil and others by demonstrating that eosinophils possess important phagocytic properties with respect both to bacteria and cells; they also showed by the use

of hydatid fluid that eosinophils are well adapted to the absorption of toxic products. In their experiments those eosinophils which had absorbed toxic material lost their phagocytic properties while these properties were retained by the neutrophilic and mononuclear cells and the hydatid liquid itself lost its antigenic power. Fiessinger recently has shown that there is a definite antitoxic leukocytic reaction and defense against the foreign proteins formed in war wounds as the result of infection and the destruction of tissue and that eosinophils are concerned in the mechanism of this defense. All of these observations lead to the conclusion that eosinophils may play an important rôle in the maintenance of immunity.

2. *The clinical incidence of eosinophilia.*—Eosinophilia has been described in association with many conditions, although in most of them the percentage is neither high nor persistent. A low grade of eosinophilia is found in some cases of scarlet fever, neurasthenia, and polycythemia. A constant slight relative and marked absolute eosinophilia is present in myelogenous leukemia. Eosinophilia also is associated with the presence of parasites and its occurrence in asthma and in certain cutaneous diseases is well established. The most marked eosinophilias which I have been able to find reported in medical literature have occurred in cases of trichinosis, in which the eosinophilia is transient, of lymphadenoma, especially associated with cutaneous lesions, and occasionally in cases of carcinoma and sarcoma. Reports of instances in which the eosinophils have even temporarily reached 25 per cent or more are exceedingly rare. I have had under observation a patient (Case 104259) with Hodgkin's disease who had an eosinophilia of 33.3 per cent with a leukocyte count of 12,000. The diagnosis was made after the excision of a gland for microscopic examination. No reason for the marked eosinophilia could be discovered. Aubertin and Giroux describe a cardiac case with cyanosis and frequent attacks of decompensation in which a persistent and very high eosinophilia was present. The leukocyte count varied from 6900 to 13,500 and the eosinophils from 57 to 68.25 per cent. Dunger reports a case of probable carcinoma of the colon in which the leukocyte count was 35,330, 60 per cent of which were eosinophils. Sibley reports an eosinophilia of 39.6 per cent and a leukocyte count of 28,150 in a case of lymphadenoma associated with cutaneous lesions.

In none of these cases was a markedly enlarged spleen present; in only one instance was the eosinophilia persistent.

3. *The occurrence of eosinophilia with hyperleukocytosis.*—After a careful study of the literature only three instances of eosinophilia associated with hyperleukocytosis have been found. Glanzmann describes a case of lymphadenoma as "lymphatic endotheliomatosis," in which the leukocyte count varied from 12,000 to 183,000 and the eosinophils from 4 to 33.6 per cent. Reinbach reports a lymphosarcoma of the cervical region, with a leukocytosis of 120,000 and an eosinophilia of 48.28 per cent. The leukocytosis was transient and the eosinophilia fluctuating in these 2 cases. Stillman, in 1912, reported to the New York Academy of Medicine a case of persistent eosinophilia with hyperleukocytosis and splenomegaly. The features of Stillman's case conform closely to those of the case herewith reported, and it is the only similar case that I found in the literature. The leukocyte count varied from 118,000 to 165,000 and the eosinophils from 85.8 per cent to 91 per cent. The spleen was slightly enlarged and the lymph nodes were palpable. The patient was under observation for a short time only and his subsequent record is unknown.

4. *The possibility of the existence of an actual eosinophilic leukemia.* Our knowledge of eosinophilia in general strongly favors the conclusion that an eosinophilic hyperleukocytosis is not a true leukemia. The occurrence of eosinophilia has so far been most satisfactorily explained on the basis of the chemotactic theory. In cases of a very chronic type of toxemia or infection it is possible that certain poisons which are effective throughout the entire organism for years may induce a persistent eosinophilia of almost any degree. It has been repeatedly demonstrated that some substances may call forth a local eosinophilia which will have no recognizable effect on the blood count. When the process is more extensive and the chemical irritant affects larger parts of the organism, or possibly when a different form of toxin is circulating, the demand for increasing numbers of eosinophils, as well as the toxin itself, may react as a physiologic stimulant to the production of eosinophils in the bone-marrow and in other hemopoietic structures. A perversion of these tissues may be the result.

In the case which has been reviewed those conditions which may be said to argue in favor of the existence of a true eosinophilic leukemia following splenectomy are as follows: (a) The persistently high leukocyte count, (b) the marked splenomegaly, (c) the general

glandular hyperplasia, (d) the gross appearance of the glands, spleen, and bone-marrow, (e) the occurrence of a small percentage of immature cells and an occasional myelocyte in the blood smears, and (f) the presence of active hyperplasia in glands, spleen, and bone-marrow together with the presence in these tissues of numerous eosinophilic myelocytes.

The facts which constitute the evidence against the existence of an actual leukemia are: (a) The marked predominance of mature and almost mature eosinophils in the blood-stream and in the hemopoietic system, (b) the postmortem demonstration of an obliterative endocarditis, perihepatitis and hepatic cirrhosis, which would account for a greater part of the symptomatology during the entire course of the disease and would indicate the probable presence of a chronic toxemia, (c) the absence of hyperleukocytosis before splenectomy, (d) the long duration of the disease, approximately seven years, and (e) the absence of the typical microscopic characteristics of leukemia.

While not entirely discarding the view that an eosinophilic leukemia may have been present at least after splenectomy, I am inclined to regard the case as an instance of eosinophilic hyperleukocytosis, the blood picture of which was remarkably altered by splenectomy. This permanent increase of the leukocytes following splenectomy for a period of four and one-half years, considered in connection with the occurrence of a more or less constant eosinophilia after splenectomy for various other conditions, may be indicative of some special function of the spleen with respect to eosinophilic cells or with respect to the toxins which eosinophilic cells are capable of absorbing.

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## **SKIN AND SYPHILIS**





## BASAL-CELL EPITHELIOMA\*

A. C. BRODERS

In the second of a series of articles on epithelioma published in 1918, MacCarty and I<sup>1</sup> classified such tumors into six types or apparent types and described each. The tumor commonly known as the rodent ulcer has been termed basal-cell epithelioma because its cells tend to differentiate to a form similar to the cells of the basal or germinative layer of the epidermis. This type, which, like other epitheliomas, may be found on any surface covered with protective epithelium, develops practically always above the clavicle. The majority of its lesions attack the cheek, the eyelids, the nose, the forehead, the ear, the canthi, and the temporal regions.

Basal-cell epithelioma often appears in the skin as an elevated, whitish nodule which resembles an adenoma or cyst of a sebaceous gland, as an ulcer with indurated borders, or as a scaly lesion. The latter type, which exfoliates its superficial layers to a shiny surface but which shows little tendency to heal completely (Figs. 257, 258, 259, 260, 261 and 262), is usually found in persons who are exposed to intense sunlight. The cells of the basal-cell epithelioma vary greatly in morphology and in arrangement. They may be long and slender, short and thick, round, oval, or spindle shaped. In arrangement they may be alveolar or gland-like and resemble the structure of the thyroid; they may present a cactus-like appearance, a diffuse or circumscribed solid mass of cells, or a combination of these different types (Figs. 263, 264, 265, 266, 267, 268, 269, and 270).

Since, as a matter of fact, all tumors arising in protective epithelium are basal-cell epitheliomas, their cellular differentiation is their

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only distinguishing feature. Because of some common characteristics, many basal-cell epitheliomas are undoubtedly diagnosed endotheliomas, alveolar sarcomas, round-cell sarcomas, spindle-cell sarcomas, and adenocarcinomas. Moreover, the cells of a pure basal-cell epithelioma are not supposed to contain prickles or spines; but because these do sometimes appear, it is often difficult to determine whether an epithelioma should be called a basal-cell or squamous-cell epithelioma, especially since prickle cells are found in so-called basal-cell

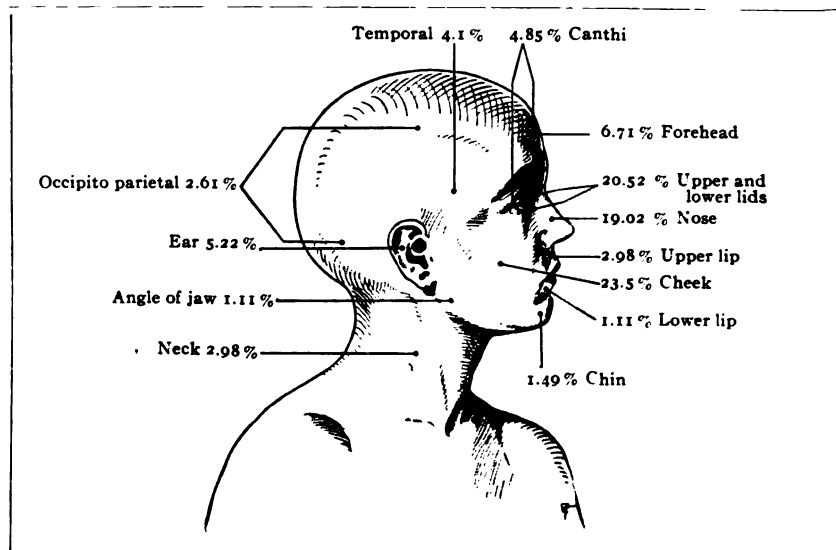


FIG. 254.—Location and percentage of basal-cell epitheliomas above the clavicle.

epitheliomas, and basal cells can always be seen in squamous-cell epitheliomas. It now seems to be a well established fact that a basal-cell epithelioma can change into a squamous-cell epithelioma, or at least into an epithelioma in which the squamous cells predominate. We know, beyond a doubt, that basal cells and squamous cells may be shown intimately connected in a neoplasm (Fig. 271), and this may account for the contention of some pathologists that basal-cell epitheliomas do occasionally metastasize.

In the series of cases here reported, none has been included without a thorough microscopic examination. In distinguishing between cases that should be classified as basal-cell epithelioma and those that should be classified as squamous-cell epithelioma, the following rule

has been adhered to: If the majority of the cells of the epithelioma are of the squamous-cell type, it is classified as a squamous-cell epithelioma; but if the majority are of the basal-cell type, it is classified as a basal-cell epithelioma.

TABLE 1.—BASAL-CELL EPITHELIOMA

		Per cent
Patients.....	268	
Percentage of 2,000 cases of general epithelioma.....	...	13.4
Males.....	165	61.6
Females.....	103	38.4
Average age, years.....	56.7	
Oldest, years.....	87.7	
Youngest, years.....	23	

FAMILY HISTORY OF MALIGNANCY

Males.....	17	10.3
Females.....	12	11.65
Total.....	29	10.82

PERSONAL HISTORY

History of previous mole, wart, pimple, eczema, scab, ulcer, etc.....	...	37.1
History of injury.....	...	9.3
Average duration of lesion, years.....	7 $\frac{1}{2}$	
Longest duration of lesion, years.....	45	
Shortest duration of lesion, months.....	3	
Average greatest diameter of lesions, cm.....	2	
Greatest diameter of lesion, cm.....	12	
Smallest diameter of lesion, cm.....	0.5	

OCCUPATION

Males:		
Farmer.....	82	56.16
Laborer.....	8	5.47
Carpenter.....	7	4.79
Merchant.....	6	4.10
Real estate dealer.....	6	4.10
Miscellaneous (26 occupations).....	37	25.38
Females:		
Farm workers.....	39	43.33

There is, however, one tumor classified by some pathologists as a basal-cell epithelioma which is not included in these statistics as we term it, a basal-cell-like epithelioma. This tumor occurs in the nose, in the pharynx, in the antrum of Highmore, in the parotid gland, in the cavity of the mouth, and in similar places. Although it is of long

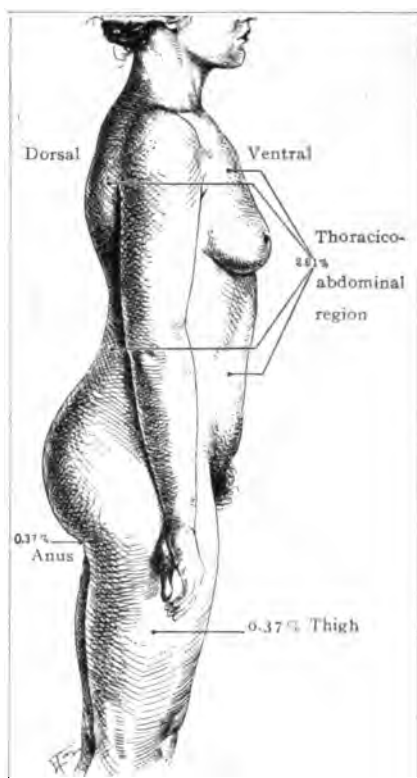


FIG. 255.—Location and percentage of basal-cell epitheliomas of trunk and thigh.

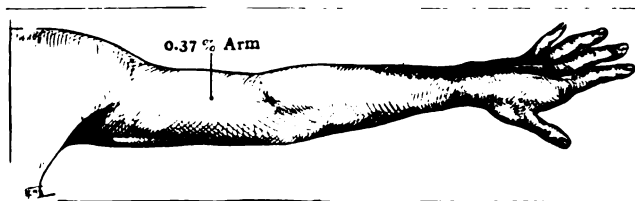


FIG. 256.—Location and percentage of basal-cell epitheliomas of upper extremity.

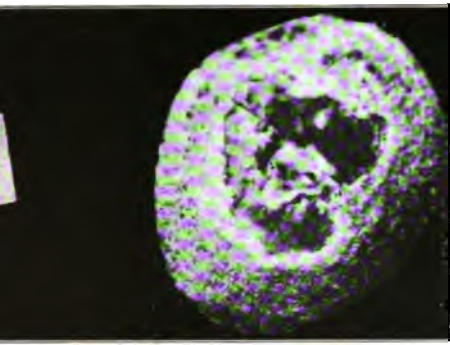


FIG. 257.—(A50531). Basal-cell epithelioma of scalp.

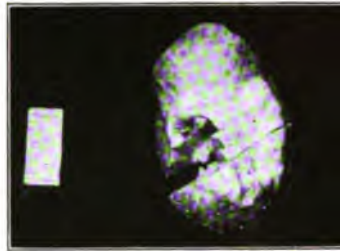


FIG. 258.—(A 55948). Basal-cell epithelioma of nose.



FIG. 259.—(A 33173). Basal-cell epithelioma of eyelid.



FIG. 260.—(A 96196). Basal-cell epithelioma of eyelid.



FIG. 261.—(A 98228). Basal-cell epithelioma of forehead.



FIG. 262.—(A 59758). Basal-cell epithelioma of cheek.

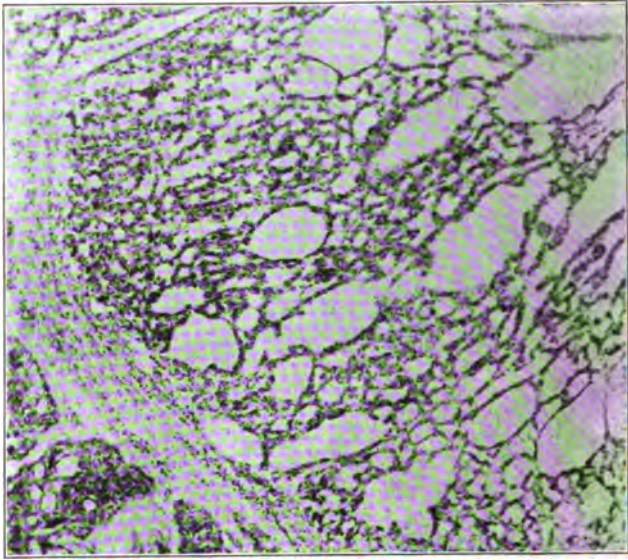


FIG. 263.—(A 38151). Basal-cell epithelioma of the outside of the nose. Note the close resemblance to thyroid.

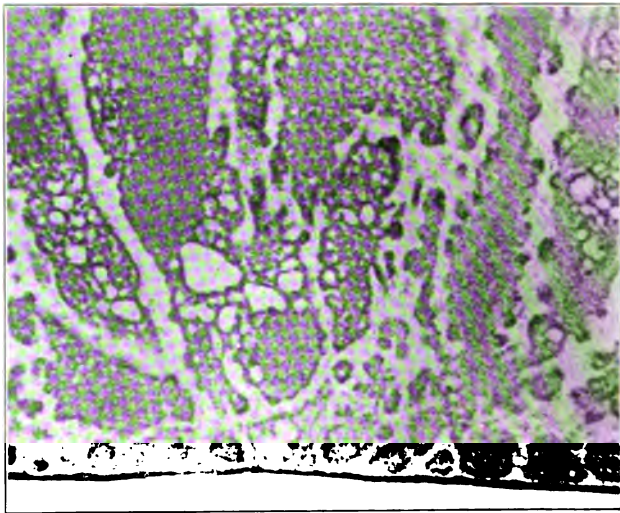


FIG. 264.—(A 33009). Basal-cell epithelioma of forehead, showing gland-like and solid areas.

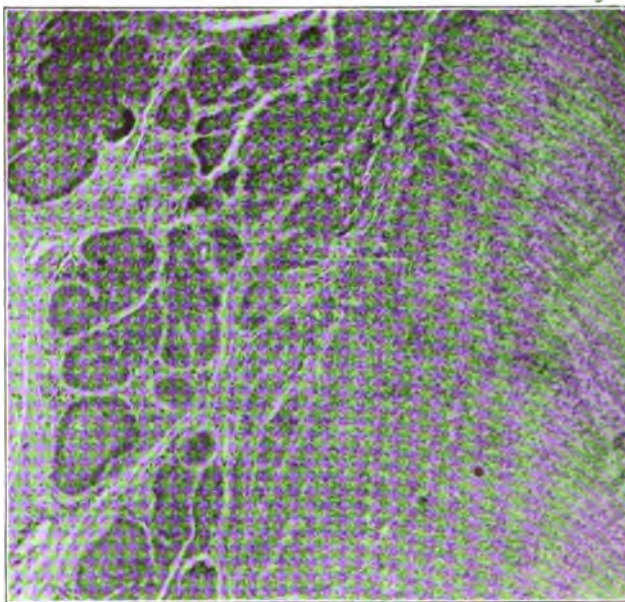


FIG. 265.—(A 38366). Basal-cell epithelioma of the nose, showing solid plugs of cells.

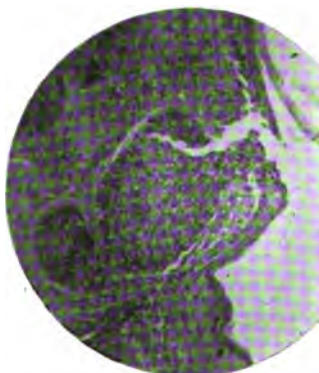


FIG. 266.—(A 71769). Basal-cell epithelioma of the cheek similar to Figure 264.





**FIG. 267.**—(A 61661). Basal-cell epithelioma of eyelid showing circumscribed and diffuse masses of cells.



**FIG. 268.**—(A 98228). Basal-cell epithelioma of forehead; same as shown in Figure 261.

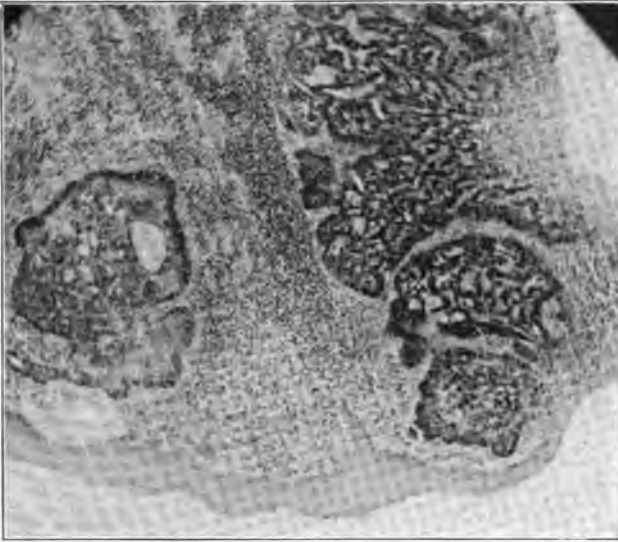


FIG. 269.—(A 38151). Basal-cell epithelioma of the outside of the nose, showing connection with epidermis; same as Figure 263.

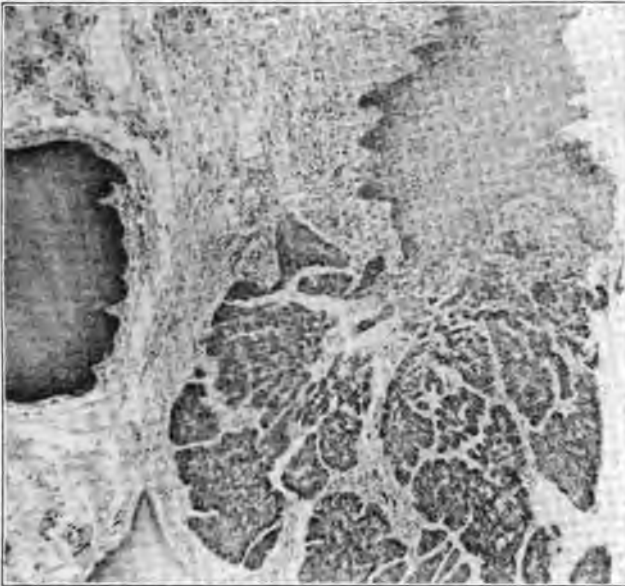
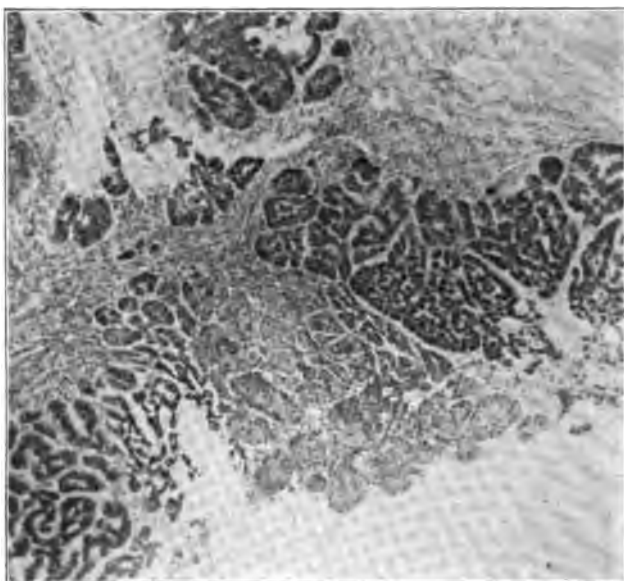


FIG. 270.—(A 20310). Gland type of basal-cell epithelioma of the outside of the nose, showing connection with epidermis.



**FIG. 271.**—(A 20310). Gland type of basal cells intimately connected with squamous cells (typical metaplasia), adjacent to microscopic field of Figure 270.



**FIG. 272.**—(A 96196). Basal-cell epithelioma of eyelid—originating from a hair follicle; same as Figure 260.

duration and has a microscopic structure similar to that of the basal-cell epithelioma, the trained eye will detect a difference; also, such tumors will metastasize, while the basal-cell epithelioma which occurs on the outer surface of the body is not supposed to do so.

In presenting this series of cases of basal-cell epithelioma, I have endeavored to classify the findings as briefly as possible, and, at the same time, to bring out the most important points. Its chief object is to present in tabulated form a collective history of the cases, so as to furnish data of the initial appearance, clinical manifestations, treatment, and ultimate fate of the basal-cell epithelioma. As the patients whose cases are tabulated here came to the Mayo Clinic between Nov. 1, 1904, and July 22, 1915, which period antedates the active use of radium in the treatment of this type of neoplasm, practically no account is given in this article of our experience with the curative properties of radium.

TABLE 2—LOCATION OF THE LESION

Single lesion.....	252	
Multiple lesions.....	16	
Cheek.....		23.5
Eyelids.....		20.52
Nose.....		19.02
Forehead.....		6.71
Ear.....		5.22
Canthi.....		4.85
Temporal region.....		4.10
Neck.....		2.98
Upper lip.....		2.98
Occipitoparietal region.....		2.61
Thoracico-abdominal region, ventral and dorsal.....		2.61
Chin.....		1.49
Angle of jaw.....		1.11
Lower lip.....		0.37
Arm.....		0.37
Anus.....		0.37
Thigh.....		0.37

TABLE 3.—TREATMENT  
PREVIOUS TREATMENT OF LESION ELSEWHERE

	Per cent
One or more treatments; acids (nitric and hydrochloric), carbon dioxid, copper sulfate, electricity, paste, radium, silver nitrate, and roentgen ray.....	27.23
One or more operations.....	20.14
Operation without being treated with acids, carbon dioxid, etc., before, at, or after operation.....	14.55
Treatment with acids, carbon dioxid, etc., without operation.....	21.64
Operation and treatment with acids, carbon dioxid, etc.....	36.19

## TREATMENT AT MAYO CLINIC

Excision with knife (one).....	48.13
Excision with knife immediately followed by cautery (one).....	26.86
Excision with cautery (one).....	4.47
Miscellaneous (knife, cautery, roentgen ray, radium).....	3.73
Excision with knife immediately followed by cautery (two or more) ...	2.98
Excision with knife immediately followed by cautery and later by cautery (one).....	2.98
Excision with knife (two or more).....	2.23
Cautery (once).....	2.32
Excision with knife followed later by cautery (one).....	1.86
Excision with cautery (two or more) .....	1.48
Cauteries (two or more).....	1.11
Inoperable.....	1.86

TABLE 4.—ULTIMATE RESULT

		Per cent
Patients heard from.....	145	54.10
Patients living.....	110	75.86
Patients dead.....	35	24.13

## CONDITION OF LIVING PATIENTS

No recurrence.....	83	75.45
Slight recurrence.....	22	20.0
No improvement.....	5	4.54

## TREATMENT IN CASES IN WHICH THERE WAS NO RECURRENCE

One excision with knife.....	38	45.77
One excision with knife followed immediately by cautery ...	24	28.91
One excision with cautery.....	8	9.62
Miscellaneous (various combinations of excisions and cauteries).....	7	8.43
Two excisions with knife.....	3	3.61
One excision followed immediately by cautery and later by another cautery.....	3	3.61
Total.....	83	
Average greatest diameter of tumor, cm.....	1.75	
Of the 83 living patients with a good result, 25 (30.12 per cent) were either operated on or treated with acid, carbon dioxid, etc., elsewhere.		

LENGTH OF TIME SINCE LAST OPERATION OR ONLY OPERATION

1 year and more	2 cases	7 years and more	5 cases
2 years and more	2 cases	8 years and more	3 cases
3 years and more	17 cases	9 years and more	3 cases
4 years and more	15 cases	10 years and more	8 cases
5 years and more	13 cases	11 years and more	1 case
6 years and more	9 cases	12 years and more	4 cases
		13 years and more	1 case
Average: 6 years, 1.6 months.		Total 83 cases	

TREATMENT IN CASES IN WHICH THERE WAS SLIGHT RECURRENCE

		Per cent
One excision with knife.....	9	40.90
One excision with knife followed immediately by cautery....	6	27.27
Miscellaneous (various combinations of excisions and cauteries).....	5	22.73
Two or more excisions with cautery.....	2	9.09
Total.....	22	
Average greatest diameter of tumor, cm.....	2	
Of the 22 living patients with a fair result there were 13 (59.09 per cent) either operated on or treated with acid, carbon dioxid, etc., elsewhere.		

TREATMENT IN CASES IN WHICH THERE WAS NO IMPROVEMENT

Miscellaneous (various combinations of excisions and cauteries; one patient refused operation and was treated with roentgen ray).....	5
Average greatest diameter of tumor, cm.....	3.75
Of the 5 living patients with a bad result there were 4 (80 per cent) either operated on or treated with acid, carbon dioxid, etc., elsewhere.	

TABLE 5.—MORTALITY

Average age at time of death, years.....	69
Oldest, years.....	91
Youngest, years.....	48
Average length of life after the last or only operation, 4 years, 3.6 months.	

## CAUSE OF DEATH ACCORDING TO RELATIVE OR HOME PHYSICIAN

		Per cent
Basal-cell epithelioma.....	11	31.42
Heart disease.....	5	14.28
Carcinoma of stomach.....	3	8.57
Apoplexy.....	3	8.57
Carcinoma of colon.....	1	2.85
Carcinoma of liver.....	1	2.85
Carcinoma of uterus.....	1	2.85
Carbuncle.....	1	2.85
Cold and bronchial obstruction.....	1	2.85
Diabetes.....	1	2.85
Gangrene of foot.....	1	2.85
Hemorrhage of throat.....	1	2.85
Unknown.....	5	14.28
Total.....	35	
Average age of patients who died of basal-cell epithelioma, years.....	59.7	
Oldest, years.....	79	
Youngest, years.....	48	
Length of life after the last or only operation, years.....	4.12	
Average greatest diameter of lesions of patients known to be dead, cm.....	2.67	
Average greatest diameter of lesions of those who died of basal- cell epithelioma, cm.....	4.32	

## TREATMENT OF PATIENTS WHO DIED

One excision with knife.....	18	51.42
One excision with knife immediately followed by cautery....	11	31.42
Miscellaneous (various combinations of excisions and cau- teries, one case inoperable).....	6	17.14

## TREATMENT OF PATIENTS WHO DIED DUE TO BASAL-CELL EPITHELIOMA

One excision with knife.....	4	36.36
One excision with knife immediately followed by cautery....	4	36.36
Miscellaneous (one inoperable).....	3	27.27

Fifteen (42.85 per cent) of the 35 patients known to be dead  
were either operated on or treated with acids, carbon dioxid,  
etc., before entering the Mayo Clinic.

## COMPLICATIONS IN THREE FATAL CASES

Carcinoma of the breast.....	1
Carcinoma of the colon.....	1
Carcinoma of the body of the uterus.....	1

## SUMMARY

1. Our present series of cases represents 13.4 per cent. of 2,000 cases of general epithelioma.

2. Basal and squamous cells can be shown intimately connected in a neoplasm.

3. It seems to be a well-established fact that a basal-cell epithelioma can change into a squamous-cell epithelioma, or at least into an epithelioma in which the squamous cells predominate.

4. Basal-cell epithelioma occurs more often in males than in females the proportion being about 3:2 in favor of the former.

5. The disease occurs in patients past middle life; their average age is 56.7 years.

6. It occurs more often in farmers than in any other class of people.

7. A family history of malignancy and a personal history of injury play a negligible part.

8. Previous mole, wart, pimple, eczema, scab, or ulcer, are associated in 37.1 per cent of the cases.

9. The duration of the lesion shows a marked variation; it extends from three months to forty-five years, with an average of seven years and one month.

10. Ninety-six and twenty-eight hundredths per cent of all the lesions occur above the clavicle.

11. Thirty-six and nineteen hundredths per cent of all the patients had been either operated on or treated with acids, carbon dioxid, and so forth, before entering the Mayo Clinic.

12. In approximately 75 per cent of all the cases treated at the clinic there was either one excision with the knife alone or one excision with the knife immediately followed by cautery.

13. Of the 54.1 per cent of patients heard from, 75.86 per cent are living, of whom 75.45 per cent report a good result.

14. In the cases in which a good result was reported, 74.68 per cent of the patients had either one excision with the knife alone or one excision with the knife immediately followed by cautery.

15. The patients who had been treated with acids, carbon dioxid, and so forth, before entering the clinic did not get so good a result as those who had had no previous treatment.

16. The low grade of malignancy of the neoplasm is evidenced by its long duration, lack of metastasis in a single case in this series,



response to proper surgical treatment, and by the fact that 75.45 per cent of the patients reported living have been free from the disease on an average of six years, one and six-tenths months.

17. Of the patients reported dead, fewer than one-third died from this disease.

18. Excessive exposure to sunlight as a cause of the neoplasm has not been borne out by the facts in our series of cases. It was noted that the hand, which is exposed to sunlight at least as much as any part of the body above the clavicles, did not show lesions.

19. Practically all the neoplasms in our series had their origin in the germinal layer of the epidermis of the skin. Only one was demonstrated to have originated from a hair follicle (Fig. 272).

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## CONGENITAL ECTODERMAL DEFECT WITH REPORT OF A CASE\*

W. H. GOECKERMANN

This case is reported not only because of its apparently extreme rarity but also because it may serve as a stimulus to further investigation of the factors responsible for defective development of the ectoderm. A convenient opportunity is also afforded to discuss certain phases of the function of the skin on which modern physiologists and dermatologists still disagree. Our case is the second of its kind reported in the American literature and the sixth reported in the world's literature.† It stands absolutely unique, however, in the fact that the developmental defect occurred in a female; all other cases reported occurred in the male. The significance of the latter fact will be apparent from subsequent discussion. It would seem, however, that the extreme rarity of this type of case is more apparent than real. All evidence in the literature points to the fact that the extremely high grades of ectodermal defect are not excessively rare. A larger number of reported cases could undoubtedly have been classified with the group under consideration had their investigation been sufficiently complete. Nor are these cases of purely academic interest as the experience of the patients and their medical advisers attest.

Cases of ectodermal defects of a partial character, such as congenital aplasia of the teeth, hypotrichosis, or even congenital absence of circumscribed patches of skin, are no longer medical curiosities. Congenital aplasia of the teeth is reported in the very earliest medical writings and numerous references to it are found in the later medical literature. True congenital hypotrichosis is distinctly more rare and the majority of cases reported as such are undoubtedly of the alopecia totalis type, in

\* Reprinted from *Arch. Derm. and Syph.*, 1920, N. S. 1, 396-412.

† Since this article has gone to press I have noted an abstract in the *Journal of the American Medical Association* for Sept. 13, 1919 (lxxiii, 879), reporting what appears to be a case analogous to those herein described. The original case report appeared in the *Nordiskt Mediciniskt Archiv*, li, 51, Oct. 18, 1918, *Int. Med. Sec.*, No. 1. To date I have not had access to the original article.

which the fetal hair is formed but later drops out and does not grow again. The work of Waelsch, Pinkus, and others, and notably the careful studies of Buschke, have familiarized us with true hypotrichosis. A combined absence of the teeth and hair is found in still rarer instances. Circumscribed skin defects of a congenital nature are reported in limited numbers. Abt, in 1917, collected 34 cases in the literature, and added another of his own. Almost any region of the skin was involved in one or the other of these cases, but the defects were most frequently noted in the scalp.

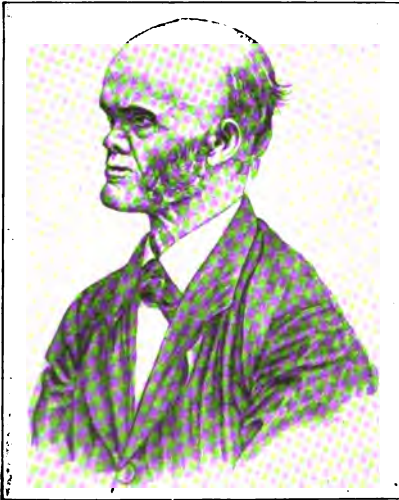


FIG. 273.—Guilford's patient. Note the prominent forehead, alopecia, and depressed nasal bridge.



FIG. 274.—Tendlau's patient. Note the features characteristic of congenital ectodermal defect. Mustache and beard well developed as in all other male patients.

In one group of cases of high grade congenital ectodermal defect reported in the literature there is not only a congenital absence of the teeth and a hypotrichosis, but also a total absence of sweat glands and an almost total absence of sebaceous glands. This combination of features gives them a stamp which places them in a class by themselves. To date there are only 5 cases of this type on record. The first of these was reported in 1883 by Guilford, an American dentist (Fig. 273). As he said, he had the pleasure of presenting a very remarkable man. The patient was forty-eight years of age, and in perfect physical health, never having been confined by sickness for a single

day. He had been edentulous from birth; he was totally lacking in the sense of smell, and almost devoid of the sense of taste; the surface of his body was destitute of the fine hair that should cover it, and he had never perspired. Tendlau, in 1902, reported a case presenting very much the same characteristics as that of Guilford (Fig. 247). He concerned himself chiefly, in his discussion, with the absence of sweat glands in the skin and erroneously interpreted the lack of development of the skin as an atrophy. In fact he heads his article: "Concerning congenital and acquired atrophiea cutis idiopathica,"



FIG. 275.



FIG. 276.

FIGS. 275 and 276.—Wechselmann's patients. Note the characteristic profile of patient in Figure 275, practically duplicating that of our patient, Figure 278.

and discusses elaborately several cases of acquired atrophy of the skin. Wechselmann and Loewy, in 1911, subjected Tendlau's case and two others to a most careful study (Figs. 275 and 276). Their investigation was devoted chiefly to the mechanism of production of insensible perspiration. Christ, in 1913, added a further case and discussed the relationship of the various ectodermal structures to one another in the animal kingdom. To this classic group we wish to add our own case.

## REPORT OF CASE

Case 240873. I.C., a woman, aged 21, born in England, stenographer, came to the clinic primarily to have some plastic work done on her nose, which was rather flat in the bridge.



FIG. 277.—(240873). Author's patient. The scalp is covered by a wig, which hides the almost total alopecia.

Examination revealed a person of a rather frail build, but on the whole presenting a fair average physical development, excepting only that of the skin and its appendages. The skin is exceptionally fair, smooth, thin, pliable and dry, and shows the superficial veins very plainly. There is a notable absence of the lanugo hair on all parts of the skin, and only a few straggling hairs are seen on the scalp. The genitalia and axillæ are practically hairless. About the labio-nasal

folks and on both upper and lower lids are a number of soft split-pea sized papules strongly suggesting small sebaceous cysts or milia. On the back are a few papules and pustules and the scar of an intramuscular arsphenamin slough. The nails of the hands and toes present uniform fine longitudinal furrows. The vermillion border of the lips



FIG. 278.—Lateral view of author's patient.

is poorly defined. Both jaws are devoid of visible teeth on physical examination. The x-ray report, however, states that several "fragments" of teeth can be seen in the right upper jaw. The patient gives a history of having had several defective teeth removed from her upper jaw; she has never to her knowledge had any teeth in the lower jaw. The rhinolaryngologist reported an atrophic rhinitis, and a destruction of the turbinates on both sides with much pus and crusting. No adenopathy could be determined. The forehead is

unusually prominent and the bridge of the nose flat (Figs. 277 and 278). Aside from these two features there were no osseous changes which even remotely suggested any of the osseous stigmata of lues hereditaria. The nervous mechanism is apparently normal, only a slight hyperactivity of the knee-jerks being noted. The mentality is very fair, probably somewhat above the average. The viscera are normal.

The patient gave a history of two aunts and one uncle having died of tuberculosis; one aunt suffered from epileptic attacks and died insane. The father was said to have had syphilis. There is no history of any other member of the family having been afflicted as is our patient. One sister died at one and one-half years of age; one brother and one sister are living and perfectly well.

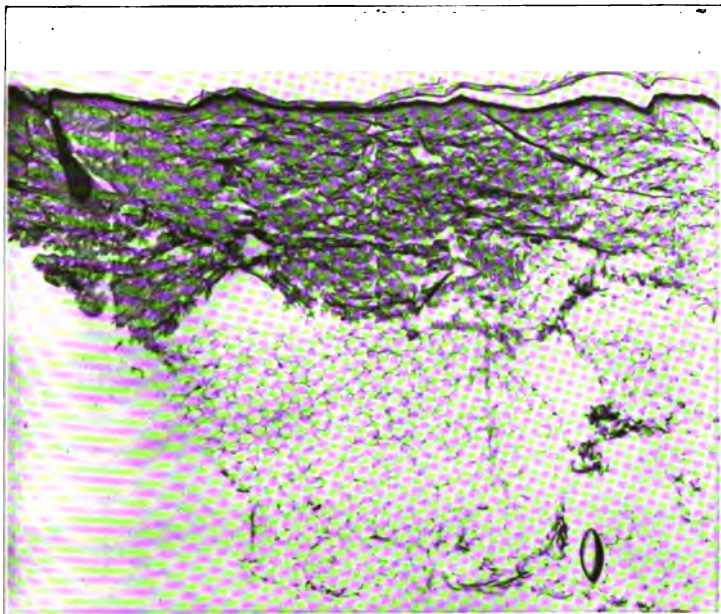
The patient began to have trouble with her nose when she was nine months old. She has never perspired even in the hottest weather. She has suffered from a variety of ailments all her life, but a definite diagnosis of her condition had not been made. For many years she has been taking medicine regularly by mouth, but has never known exactly what for. She has had two salvarsan injections, evidently on the supposition that she was afflicted with lues hereditaria.

*Histologic report.*—The patient after some persuasion submitted to biopsy. The tissue was taken from the outer aspect of the left arm; the piece at least three-fourths of an inch in length was excised deep into the subcutaneous fat. While we realize that in theory the total absence of hair, sebaceous glands, and sweat glands can be demonstrated only by an examination of a number of pieces of tissue from different parts of the body, such an examination in this case was out of the question.

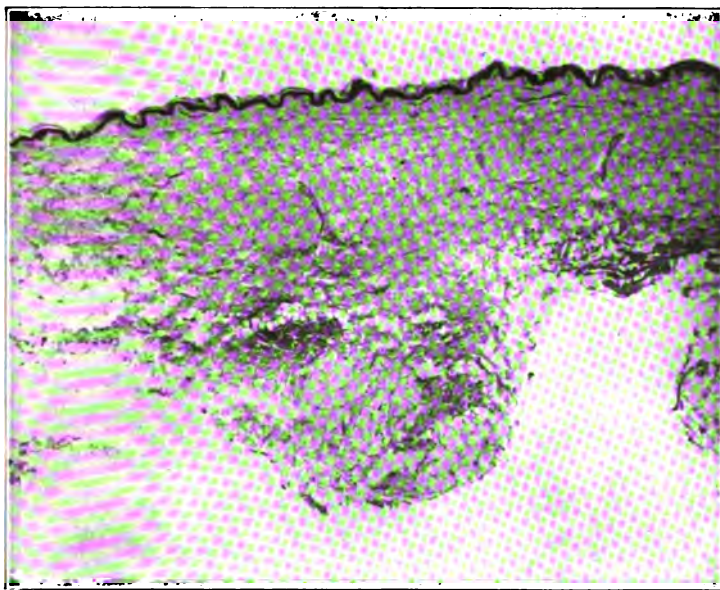
For purposes of comparison an exactly similar piece of tissue was taken from the skin of the outer side of the arm of a normal adult female (surgical amputation). In order to identify and compare the anlagen of the pilo-sebaceous and sudoriferous systems in the human embryo a specimen was taken from the outer sides of the left arms of human embryos of 5 cm., 7 cm., 10 cm., and 25 cm., and from a fetus at seven months.

The epidermis and cutis of the patient were absolutely normal as compared with a section of normal skin, except for the total absence of hair follicles, sebaceous glands, and sweat glands. The cutis in the case of extodermal defect displayed a normal vascularity, made artificially conspicuous by the absence of the usual association with





g. 279.—Section from the arm of a healthy woman. Note the presence of sweat glands and the hair follicle.

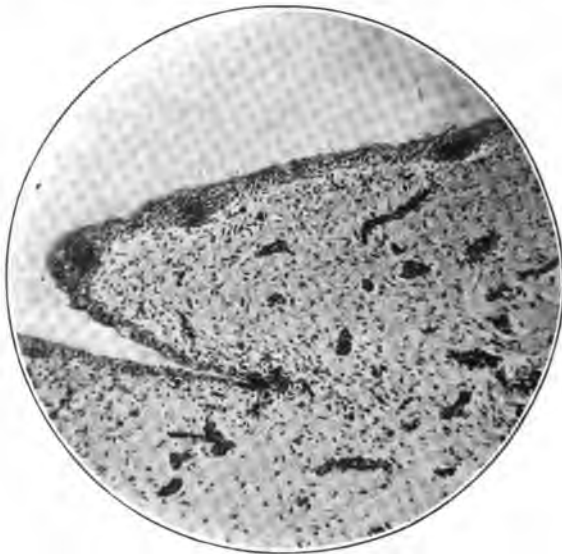


. 280.—Section from the arm of our patient, showing total absence of the sudoriferous and pilo-sebaceous systems.





**FIG. 281.**—Section from the arm of a seven months old fetus. The sweat glands and hair follicles are not yet fully developed, but they show plainly.



**FIG. 282.**—Section from the arm of a 10 cm. fetus. Note the epithelial buds.

pilo-sebaceous and sudoriferous structures. There were no increase or diminution in the collagenous or elastic tissue of the cutis, no signs of an inflammatory process, no abnormal elongation of the occasional rete pegs, and no cellular infiltration of any type. The sections show the tissue far into the subcutaneous fat. There were no cell inclusions, either solid or tubular, of the type generally recognized as anlagen of sweat glands in the familiar picture of syringocystoma (Fig. 280).

The comparison of the skin of the fetal arm with that of our patient indicates that in the site from which the specimen was excised there

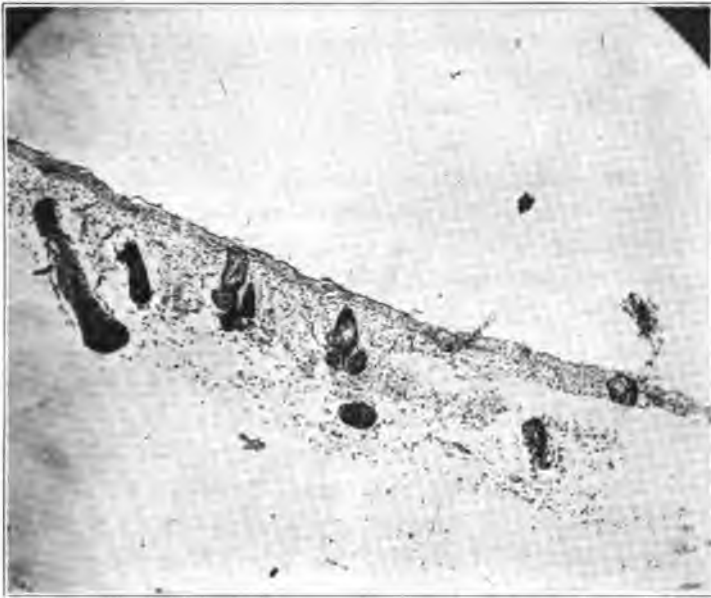


FIG. 283.—Section from the arm of a 25 cm. fetus. The immature sweat glands and hair follicles are clearly shown.

are in late fetal life and immediately after birth many lanugo hairs with their associated sebaceous glands, and numerous sudoriferous glands which have not quite reached their final development by the seventh month of fetal life (Fig. 281). The various structures representing the anlagen of these glands, as illustrated in Figures 282 and 283, were carefully searched for in the material from our patient, but as seen in the photomicrograph (Fig. 180) they were totally absent.

In the histologic material, therefore, we find that the pathologic process in such a patient is neither an atrophy nor a simple rudimentary

development, but consists in a total absence of pilo-sebaceous and sudoriferous systems and their anlagen, at least in adult life. Whether at some stage in the embryonic development in our patient such anlagen appeared only to undergo regression or to be destroyed, it is of course impossible to state with positiveness from an examination of a specimen removed from the adult.

#### DISCUSSION

Wechselmann believes that congenital ectodermal defects of the type presented by our case are familial and inherited, and are analogous to the type of hereditary transmission seen in hemophilia and hemeralopia. The analogy may be allowed in so far as these diseases are transmitted through the female, but the defect need not always be transmitted to the male, as our case plainly shows. In other words, these congenital defects are not always recessive in the female. Whether or not hemophilia and hemeralopia are always recessive in the female is still a problem, despite the careful studies of Bulloch and Fildes. The familial transmission of the ectodermal defects is well shown by a family tree compiled by Wechselmann for his cases. From these findings this author wishes to prove the recessive character of the ectodermal defect in the female. Our own case evidently disproves this supposition. Christ's case apparently also bears out the theory that this condition is familial. A familial history was not elicited in our case, possibly because of the insufficiency of the data obtainable. Most of the reported cases of ectodermal defect, like those of hemophilia and hemeralopia, are in the families of exceptionally fertile women. In Guilford's case the mother of the patient had married at sixteen and died at forty, and during that time had given birth to twenty-one children. The mother of Tendlau's patient gave birth to fifteen children in two marriages, and the mother of Wechselmann's patients also bore fifteen children. This fecundity of the mothers of patients is not apparent in Christ's case nor in our own, each of these mothers having given birth to four children.

Syphilis as a causative factor deserves special attention. Familiarity with this striking group of cases, which present practically identical features, would hardly warrant an assumption of activity of the *Spirocheta pallida* as it appears in the ordinary case of lues hereditaria. The activity of the spirochete in ectodermal defect could be explained only by assuming that the injurious influence

had been suddenly exerted at the time of the third or fourth month of embryonal existence and had then rapidly subsided, which would seem rather unlikely. Christ reports that his patient was without doubt infected with syphilis. He does not say on what grounds he bases this assumption; the Wassermann reaction on the patient's blood was negative on one occasion. In discussing his case, he admits that he was at first inclined to believe that the developmental defect was of syphilitic origin. On discovering the familial tendencies, however, and on careful consideration of our present day conception of the genesis of congenital syphilis, he later came to the conclusion that syphilis is not a causative factor. In our case the history is rather suggestive of a syphilitic factor. The patient's mother told her that the father had acquired syphilis while serving in the British navy. The patient herself had been treated for syphilis, but evidently chiefly on the basis of the changes found in the nose, and probably by some one ignorant of the existence of the type of congenital defect under consideration. There were no other signs suggestive of lues hereditaria except those equally characteristic of this group of defects. The Wassermann test of the blood was negative. If syphilis was present in Christ's case or in our own, it was probably only incidental.

Guilford does not discuss the pathology of the skin of his patient. Tendlau in a description of the skin of his patient speaks of an atrophy, and in his report elaborately discusses other cases of cutaneous atrophy. In one paragraph he carefully notes, however, that nowhere does he see any regressive changes such as atrophy. Moreover, he concedes that there are no rudimentary nor partially developed sweat glands to suggest that the anlagen of these structures had ever existed. Wechselmann insists that there is no sign of atrophy in the skin but that it resembles the embryonal type. In our case there were no signs of regressive changes in the skin. There was an entire absence of such cell inclusions as might warrant an assumption that embryonal vestiges of lanugo hair and sweat glands had ever existed. A striking feature in this group of ectodermal defects is the hypotrichosis described by all observers. Our patient's scalp contained only a few tufts of straggling dry hair. The genitalia were also practically devoid of hair and the lanugo hair was absent over the entire body. The aplasia of the teeth has been noted in all cases and such teeth or dental "emboli" as there are occur in about the same part of the upper jaw,

as in our case, probably replacing the incisors and canines. In the lower jaw, in all cases studied by x-ray, teeth and the anlagen of teeth were completely absent. Wechselmann's article is illustrated by photographs of plaster models of the jaws, and copies of his illustrations are reproduced here (Fig. 284). Such teeth as there are, are broad at the base, and pointed at the tip, showing a close resemblance to the canine teeth. They are widely separated. Our patient had never had a tooth in her lower jaw, and the upper teeth were imperfect and had been removed. The x-ray showed "fragments" of teeth in the right upper jaw.



FIG. 284.—An illustration of Wechselmann's plaster model of the jaws and dental "emboli" of one of his patients.

The gross characteristics of the skin are in all instances very similarly described by the various authors. The skin is said to be thin, pliable, dry, unusually white and transparent, with marked prominence of the superficial veins. The mouths of the follicles are distinctly visible in some locations but not in others.

Wechselmann noted a few milia about the nose in his cases. These general characteristics of the skin were apparent in our patient and we also noted the milia about the nose. Christ describes a condition in the nasal and orbital region of his patient, which reminded him of a xeroderma pigmentosum; Touton, who saw this patient, was also reminded of the same disease, but only in a mild form. This condition was not described in any of the other patients nor was it seen in our own.

The nails of Tendlau's patient were well developed. Wechselmann notes that in one of his patients the nails were normal. A definite trophic deformity of the nails was noted in our patient; its etiologic basis is unexplained.

Atrophic rhinitis was present in the patients described by Tendlau, Wechselmann and Loewy, and Christ. Guilford does not describe this condition, but he specially mentions the fact that his patient had lost the sense of smell and largely that of taste. In our patient a well-marked atrophic rhinitis, with atrophy of the mucous membrane of the pharynx and larynx, was noted, the latter producing a distinct hoarseness. In addition to this a nasal examination revealed destruction of the turbinates on both sides with much crusting, probably a result of secondary infection.

The vermilion border of the lips in our case was not so sharply defined as in the normal person. This detail is not specifically noted in any of the other cases.

Prominent frontal bosses and a depressed nasal bridge are the chief bony changes, as all the pictures well show. 'Our patient came for treatment primarily to have the shape of her nose improved. A plastic operation was attended by a considerable degree of success.

The feature which distinguishes this group of cases of ectodermal defect from all others is the total absence of sweat glands and the almost complete absence of sebaceous glands. On this defect are based the symptoms which give them their special practical and theoretic interest. All the patients state that they do not perspire even in the hottest weather, and to this our case is no exception. Guilford's patient was a cobbler by trade and lived in a farming community. During the summer months he worked with different farmers as a field hand. Whenever so employed it was always necessary to engage a boy to carry water from some neighboring brook or well to pour over him to keep his clothing wet. If the arrival of the water happened to be delayed he became weak and collapsed from the heat. Tendlau's patient wore a wet shirt during the hot months. This he kept continually moist under a pump. When the heat became too great he frequently collapsed. This patient from childhood had been in the habit of eating only cold meals during the hot weather because he had noticed that he became feverish on the ingestion of hot foods. A similar story is told by the other patients and all of them were forced to change their original occupation because they could not tolerate heat. Because of these peculiarities one of Wechselmann's patients was temporarily regarded as a malingerer and the other as suffering from phthisis. Our patient, while she could not

perspire, suffered less hardship probably because as a woman she was less subject to exposure and hard physical work.

The mental condition of Guilford's patient was reported as normal; the patients of Tendlau, Wechselmann and Loewy, and Christ were of a distinctly inferior mentality; our patient was of average mental acuity if not somewhat above it.

Congenital ectodermal defect apparently does not interfere with the longevity of the patient. Guilford's patient was 48 when his case was reported. Wechselmann studied the patient originally described by Tendlau when the patient was 57 and in good general health.

Much interesting experimental work has been done on these cases and much light thrown on the physiology of the skin. Vierordt estimates that the relative values of different modes of heat loss are about as follows:

By urine and feces.....	1.8 per cent
By expired air; warming of air.....	3.5 per cent
By evaporation of water from the lungs.....	7.2 per cent
By evaporation from skin.....	14.5 per cent
By radiation and conduction from skin.....	73.0 per cent

Of course these percentages vary somewhat with the surroundings, but they tend to emphasize the importance of the skin as a heat regulating organ. While it is true that the lung normally dissipates the greater part of the heat in some of the lower animals, and does so very effectually in others, in man this function of the skin is apparently vicariously taken up by the lung in only a very unsatisfactory manner. The cases of ectodermal defect previously reported have shown beautifully the relationship that exists between the lungs and the skin as heat regulating organs and have offered ideal conditions for experimentation. Tendlau and Loewy have definitely shown the importance of the skin as a heat regulator and the inability of the lungs vicariously to assume this function in man.

On one occasion Tendlau's patient, on drinking a pint of milk at 104° F, was observed to undergo a rise of temperature of 0.4° within five minutes, followed by a further rise of 0.9° within the next fifteen minutes. The temperature then gradually dropped to its first level. Very noticeable were also the rises in temperature following exposure to the sun. On a perfectly quiet day the temperature rose at the

rate of  $1.8^{\circ}$  F. every ten to fifteen minutes. This rate was increased by physical exertion, extreme degrees of heat, and an increased humidity. On one occasion the patient was exposed at 12 o'clock noon while the air temperature was  $89.6^{\circ}$  F. After an exposure of twenty minutes to the sun the body temperature rose  $3.7^{\circ}$  F. Simultaneously mild subjective symptoms appeared, such as are seen in a febrile person, that is, slight restlessness, sensation of heat, and headache. Similar experiments were repeated frequently, always with the same results. The highest temperature observed on this patient was accidentally obtained on a hot day. It rose on this occasion to  $105.4^{\circ}$  F.

Tendlau, by the observations on his patient, was reminded of the behavior of poikilothermic animals. He therefore determined if possible to obtain the temperature changes in the opposite direction by applying cooling procedures. Prolonged cold baths were used, but no abnormal reduction in temperature was observed. Similar experiments were carried out by Loewy on his patients with similar results. Both observers carefully watched the respiratory function in the persons in whom an increased amount of heat dissipation was made necessary by the experiments. Tendlau's patient was carefully examined by Zuntz relative to his respiratory behavior under these conditions. Zuntz found an increased respiratory volume and rate at all times, analogous to the results obtained in non-sweating animals. Loewy confirmed these findings by further experiments.

In an endeavor to determine the absorbing power of the skin of such a patient Tendlau employed two methods. In both instances he used a potassium iodid ointment, which in all probability does away with the objection that some of the drug was absorbed by inhalation. When this ointment was applied loosely under a bandage no absorption of the potassium iodid occurred. On the other hand, when the ointment was rubbed into the arm and the arm bandaged, potassium iodid could be demonstrated in the urine in about six hours, which is no marked variation from the normal. Tendlau's first experiment tends to show that a certain amount of friction is necessary to produce any absorption. His experiments did not determine whether or not a certain amount of trauma is necessary to produce absorption, because it is impossible to say after thorough friction that the skin has not been sufficiently traumatized to produce a histologic break.



The mercurial inunction experiments performed by Wile and Elliot on patients, and on rabbits by Schamberg, apparently definitely settle the fact that there is absorption through the skin when ointments are rubbed into it. Many other observers believe that oily preparations are quite readily absorbed through the skin. Because of the total absence of sweat glands and the probable total absence of sebaceous glands on the arm of Tendlau's patient the findings in his inunction experiments constitute experimental evidence that the glands of the skin are certainly not essential and in all probability not necessary to the absorption of drugs in the normal person.

Merely as an illustration of the wide divergence of opinion on the mode of absorption of substances through the skin Landois on the one hand believes that the mercury globules pass into the hair follicles and ducts of the glands, where they are affected by the secretion of the glands and transformed into a compound capable of absorption. This view is supported by Neumann, and Auspitz, and concurred in by Duhring, Robinson, Stelwagon, and others. On the other hand, Rindfleisch, Fleischer, Voit, and others believe that the particles of mercury pass directly through the epidermis. This latter view seems most strikingly supported by the observation of Voit, who found globules of mercury between the layers of the epidermis and in the corium of an executed criminal, into whose skin mercurial ointment had been rubbed previously.

With reference to the question of the mechanism of perspiration, on which these cases throw some light, physiologists are well agreed that sensible perspiration is a true secretion, a product of the sweat glands. On the production of insensible perspiration, however, they have disagreed ever since the discovery of the sweat glands by Malpighi and Stenson. The arguments pro and con brought forth by various observers in support of their views need not be discussed here. Suffice it to say that in a considerable number of modern text-books on physiology and dermatology a discussion on the mode of production of the insensible perspiration is either entirely omitted or no decided stand is taken with regard to it.

The experiments undertaken by Loewy on Wechselmann's patients with a total absence of sweat glands tend to substantiate the marked importance of the physical process of transudation as a factor in the loss of moisture by the body under ordinary conditions. By carefully controlled experiments Loewy found that under conditions in which

only insensible perspiration could be given off, the 2 patients with ectodermal defect eliminated a minimum of 123 gm. and 242 gm., and a maximum of 436 gm. and 600 gm., respectively, as compared with an average minimum of 112 gm., and an average maximum of 700 gm. in five healthy persons. This result substantiates the fact that so long as the water is given off in an insensible manner, the quantity of water given off by the healthy person is no greater than that given off by those without sweat glands. The sweat glands, therefore, are not perpetually active, but only become so under special stress. Diffusion and not secretion is, therefore, the primary method of water elimination through the skin. Loewy further demonstrated on his case by the method of Aubert that there is a point at which perspiration is still insensible but at which the sweat gland takes some part in its production. This point varies in different persons and also on different parts of the body in the same person. It was impossible to carry on physiologic experiments on our patient, largely because of her indifference.

#### CONCLUSIONS

1. There exists a group of typical cases of high grade congenital ectodermal defect, extreme rarity of which suggested by the scanty literature is probably more apparent than real.
2. The patients in this group all present a facies very closely resembling that of heredo syphilis.
3. The influence of syphilis in the production of these congenital defects is probably nil.
4. The reported cases of this group of ectodermal defects have exhibited a total absence of sweat glands, an almost total absence of sebaceous glands, a hypotrichosis with absence of lanugo hair, and a dental aplasia.
5. Such patients suffer from a disturbance of the heat regulating mechanism, dependent on the inability of their skins to eliminate the necessary amount of water to keep the temperature level constant under varying external conditions.
6. Valuable contributions to our conceptions of certain phases of the physiology of the skin have been made by experiments on patients with this type of congenital defect.

The writer wishes to acknowledge his indebtedness to Dr. J. H. Stokes, Chief of the Section of Dermatology and Syphilology, for assistance in the arrangement of this material.

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# **SYPHILIS IN RAILROAD EMPLOYEES\***

## **A Clinical Study of an Occupational Group**

**J. H. STOKES AND HELEN E. BREHMER**

The writers have been for some time under the impression that syphilis is an exceptionally common disease among railroad employees and that it constitutes a grave and unrecognized menace to their personal welfare and industrial efficiency, and to the safety of the traveling public. In order to ascertain the statistical basis for this impression a review of 3000 unselected histories of Mayo Clinic patients was made with a view to comparing the amount of syphilitic infection in railroad men with that of certain other occupational types. Of these histories 1657 were grouped under occupational heads fairly representative of the average American citizen. The 1657 cases included men and their wives, 1148 of the former and 514 of the latter. The presence of syphilis was demonstrated in these cases by a searching examination in the Section of Dermatology and Syphilology following the routine general examination. In connection with the general study a special study was made based on the records of 50 syphilitic railroad employees, taken at random from the files of the Section, with a view to determining if possible the types of late complications most prevalent among them and the methods best suited to the detection of the disease in their examination.

Table 1 presents the relative portions of syphilitic infection in the general occupational types considered:

**TABLE 1**

	Men only		Husbands and wives	
	Cases	Per cent syphilis	Cases	Per cent syphilis
Railroad employees .....	128	11.7	184	10.3
Laborers.....	243	6.1	297	6.9
Business men (tradesmen, merchants).....	236	3.8	311	3.2
Farmers.....	536	1.5	865	1.4

\* Reprinted from Jour. Indust. Hyg., 1920, i, 419-427.

It would be inaccurate to conclude that because a given percentage of the sick have syphilis, the same percentage would hold in a through and through survey of sick and well. It seems probable, however, that the prevalence of a chronic and often latent infection such as syphilis can be more fairly estimated from a study of the sick than can that of an acute infection. The percentage of latent and concealed as well as active cases in industrial groups will perhaps bear a close relation to the share of the disease in the production of their ill health. It would appear from this table that syphilis is approximately eight times as prevalent in railroad employees as in farmers, twice as prevalent as in common laborers, and three times as prevalent as in merchants and tradesmen. An interesting sidelight is thrown by these figures on the prevalence of syphilis in general as detectable by general medical examination. Currently accepted estimates based on the clinical judgment of syphilographers of large experience represent the disease to be present in from 10 to 15 per cent of the adult population. In hospital patients currently accepted surveys based on the Wassermann test average 19.2 per cent.<sup>1,4,6</sup> Our results showed that only 3.1 per cent of syphilis was detected in our patients when subjected to general medical examination. Of 1143 men 4.2 per cent had syphilis; of the 514 women 2.6 per cent had syphilis.

It should be emphasized that the first step in the detection of syphilis in our cases was medical examination and not the routine Wassermann test. We feel that there is very little doubt that had a routine instead of an optional test been employed, the percentage recognized would have been higher. At least part of the discrepancy between our figures and those quoted is therefore attributable to the weakness of unaided clinical judgment in the recognition of this disease. An uncertain portion of the discrepancy must, however, be attributed to the very large rural factor in the clientele of the clinic. There can be no doubt that the proportion of syphilis among our patients is reduced by the large proportion of farmers seen, among whom the disease is apparently relatively infrequent. The clientele of the Mayo Clinic is drawn, moreover, quite largely from those portions of the country in which the percentage of venereal infection is low, as indicated by the recently published geographical survey of the second million drafted men.<sup>5</sup> The results of Wassermann surveys (on which high estimates are based) probably include an uncertain though small percentage of false positive results. Taking these various considera-

tions into account it seems to us not unreasonable to conclude that had we employed a routine Wassermann test on all patients our percentage of syphilis recognized would have been higher, although not so high as the estimates compiled from the clientele of city hospitals and dispensaries.

Attention has been called in the literature from time to time to the menace of syphilis of the central nervous system to the safety of the public, particularly when it takes the form of paresis and epileptiform seizures in men responsible for the operation of trains. Knapp discussed 2 cases of this type. Camp, before the Neurological Section of the American Medical Association, presented a study of epilepsy and paresis in railroad employees in which, after detailing 5 cases, he showed that of 87 admissions to the State Hospital at Kalamazoo, Michigan within a given period, 13 were of men employed in the operating department of railroads, 5 of whom were engineers.

The 50 railroad employees\* whose cases were considered in our special survey included locomotive engineers, firemen, brakemen, switchmen, conductors (excluding dining car), section hands, yard foremen, inspectors, telegraph operators, signal maintainers and station agents. Men of these types, aside from the responsibilities which devolve on them, form an especially interesting occupational group medically speaking because they have for years been ostensibly under medical surveillance, and their health record is, therefore, in a sense indicative of the efficiency of the industrial medical practice of the past. To find so high a percentage of the men infected with a grave disease, capable of seriously impairing their efficiency, and through that impairment of bringing discredit on railroad administration and danger to the public, is a matter for concern. To find so much of the infection easily recognizable, and yet apparently unrecognized, suggests the need for a modern revision of methods and conceptions in medical supervision.

Of the fifty men considered: One-third (36 per cent) were on the engines. Three-fourths (76 per cent) were engaged in the actual operation of trains (this includes engine crew). One-fourth were engaged in such occupations as yard foreman, section hand, and telegrapher.

The sexual habit of the men concerned may be inferred from the

\* See appendix to this article, in which the result of a duplicate survey is given, confirming the results in the first group.

fact that of 42 from whom data were obtained, 80 per cent admitted at least one attack of gonorrhea.

The possible contributory effect of alcohol both to infection and complications is suggested by the fact that 61 per cent were users, and 36 per cent more than occasional drinkers.

The effect of syphilis and gonorrhea on the second generation in the group considered is suggested by the fact that of 36 marriages 44 per cent were either sterile (22 per cent) or marred by miscarriages (22 per cent).

The very limited value of a history of infection in detecting the presence of syphilis, on account of the tendency to masked onsets, is forcibly illustrated by the fact that 24 per cent of the 50 syphilitics could give no history of infection other than gonorrhea. There were no recognizable secondary manifestations in 62.5 per cent. It should be accepted as axiomatic that the search for syphilis in a patient, and in members of an industrial group, must be *brought to the patient*. To wait for the individual to seek advice directly exposes him to the risk of late complications, and to errors in diagnosis, all dependent on the unreliability of the subjective account where no symptoms may appear in the period intervening between infection and accident. Observations such as these serve to illustrate concretely the weak points of clinical examination when (as is too often the case in syphilis) the clinician relies on the history for his clue.

The age data on the cases furnished two interesting observations. One-fourth of the patients (26 per cent) were infected between the seventeenth and twentieth years, one-third (32 per cent) between the ages of 20 and 25. By their twenty-fifth year nearly 60 per cent were infected; by their thirty-second year 91 per cent were infected. It seems a practical suggestion, therefore, that since the efficiency of the Wassermann test is highest in the early years of the infection, the test could be applied to best advantage to the age group 17 to 25 (60 per cent of infections) on entering railroad service, and repeated in the same group on reaching age 31 (91 per cent of cases).

The age at which relief for late symptoms is sought suggests the age group which at the present time, at least, should be subject to closest surveillance. Over one-third (34 per cent) of the onsets of late complications were in the five-year period from the sixteenth to the twentieth year after infection, as against only 45 per cent in a fifteen-year period among the remainder. Only 17 per cent of late accidents

developed after the twentieth year, and only 8.5 per cent before the sixth year after infection.

If, therefore, 91 per cent of infections occur between the ages of 17 and 21 and 71 per cent of late accidents occur in a fourteen-year period between six and twenty years after infection, it would seem that oversight to prevent late accidents should not extend to the old men who are too often the recipients of special attention, but mainly to men over 23 and under 45. Nearly 70 per cent of the men included in this series appeared for examination in the clinic before reaching the forty-fifth year, and one-third between the ages of 35 and 40. Yet 2 great railroad systems do not begin routine annual examinations until the employee reaches fifty years of age, and 6 of 8 content themselves with examination once in three years during the very period when syphilis in their personnel is most likely to endanger the lives of public and employees.

The seeming lack of connection between the presenting symptom and the actual disease process has always been a stumbling block to the recognition of syphilis by the general examiner. It was, in this series, responsible for many diagnostic errors. The dangers of the habit of grasping uncritically and unsuspectingly at the chief complaint instead of seeking the diagnostic sign are well illustrated by Table 2, representing the subjective or symptomatic side of an overwhelming preponderance of grave central nervous system and cardiovascular syphilis.

TABLE 2.—PRINCIPLE SYMPTOMS

	Per cent
1. Gastric symptoms.....	28 (vomiting 10 per cent)
2. Complaints not suggesting syphilis (such as hernia, constipation, broken nose, etc.).....	18
3. Headache and head pain.....	16
4. Cardiac symptoms (pain, dyspnea, palpitation).....	14
5. Diplopia and poor vision.....	14
6. Malaise, weakness.....	12
7. Shooting pains.....	10
8. Bladder symptoms.....	10
9. Nervousness.....	8
10. "Do I have syphilis".....	8
11. Laryngeal symptoms.....	8 (4% supposed tuberculosis)
12. "Rheumatism".....	4
13. Ataxia.....	4
14. Girdle pains.....	4
15. Dizziness.....	2



Nearly half (45 per cent) of the cases in this series were not diagnosed or were misdiagnosed before the patients entered the clinic, and of these all but one were late cases. Of the 55 per cent correctly diagnosed at some time as having syphilis, nearly half had been identified at a time when the diagnosis could scarcely have been escaped, that is, in the primary or secondary stage. It is difficult to avoid the belief that the lack of a history and the irrelevancy of some presenting symptom on which the examiner is over-prone to rely materially contribute to the percentage of error.

The blood Wassermann reaction, the first great objective diagnostic ear mark of syphilis in the general medical examination, was strongly positive in only 43 per cent of our series. Four per cent were weakly positive. Fifty-three per cent of the cases were completely Wassermann negative on the blood. There is nothing in this group to controvert the idea that Wassermanns taken on younger men (all but 8 of our cases were more than 32) would yield a higher percentage of positive results if not obscured by treatment. There is much in these figures to discourage an uncritical reliance on the negative blood Wassermann as evidence of the absence of late syphilis.

The examination of the spinal fluid proved of more value than did that of the blood in the detection of syphilis in this group. Such an examination was made in only 33 of the 50 men, but should, we are now convinced, have been made in all of them. Nearly two-thirds (64 per cent) had fluids positive on some one of the four points of the examination (increased globulin alone was not accepted as evidence) as contrasted with 47 per cent positive on the blood. The cerebrospinal fluid findings did not parallel the symptomatology in degree, nor did the symptoms necessarily suggest involvement of the nervous system. Men were accordingly found to be actively at work on engines and in other responsible positions whose cell counts ranged as high as 139.

The purely laboratory procedures contributed 58.7 per cent of the diagnoses. The remaining 41.3 per cent were identified by the methods of routine physical examination. Among these, the recognition of pupillary abnormalities and fundus changes in the eye, the signs of cardiovascular involvement, and the neurologic changes stood out preëminent.

Of 39 men, adequately examined from every standpoint that modern knowledge could suggest, 79.5 per cent had syphilis of the

nervous system; 18.7 per cent had cardiovascular syphilis. The two co-existed in some cases. Some of the cardiovascular cases were not subjected to spinal puncture, although there is no doubt in our minds at the present time that puncture should have been done.

Cardiovascular abnormalities were recognizable as valvular lesions, aortitis, myocardial changes and their sequelæ in 18.7 per cent.

Pupillary abnormalities, muscular paralyses and fundus changes proved to be among the most significant and valuable of signs, being present in 62.5 per cent of the cases. The eye findings are classified in Table 3.

TABLE 3.—EYE FINDINGS

"Slow" reflexes.....	25	per cent of 48 cases
Argyle-Robertson pupils.....	37	per cent of 48 cases
Unequal pupils.....	14.5	per cent of 48 cases
Irregular pupils.....	14.5	per cent of 48 cases
Muscular paralyses.....	12.5	per cent of 48 cases
Fundus changes.....	26.5	per cent of 34 cases

The presence of so high a percentage of abnormal eyes in a group of men whose eyes, of all the structures in their bodies, are ostensibly subject to the keenest scrutiny by railroad medical examiners was a matter for astonishment. The inadequacies of the average railroad medical eye examination, which seems to be confined to vision and color sense, and the remedial possibilities, suggest themselves at once. At least a clue to the presence of two-thirds of the syphilis we recognized in railroad men could have been had by so simple a procedure as the careful taking of pupillary reflexes.

Even an extremely simple neurologic examination, such as should properly be a part of any significant medical examination, revealed interesting facts. Omitting the details of the complete neurologic studies made on many of the cases by the Section of Neurology, the gross findings are summarized in Table 4.

TABLE 4.—GROSS NEUROLOGIC FINDINGS

Abnormal knee reflexes.....	65.1	per cent of 43 cases
Abnormal Achilles reflexes.....	78.1	per cent of 32 cases
Positive Romberg.....	38	per cent of 39 cases
Speech defect.....	15.7	per cent of 38 cases
Mental symptoms (diminished attention, irritability, amnesic attacks, etc.).....	38.4	per cent of 39 cases
Bladder involvement (cord, bladder, retention, incontinence, etc.).....	47.5	per cent of 40 cases
Ataxia.....	36.8	per cent of 38 cases
Paresthesias.....	55.8	per cent of 34 cases
Hemiplegia.....	7.1	per cent of 42 cases
Loss of consciousness.....	7.1	per cent of 42 cases

The high percentage of mental symptoms is especially interesting. Two patients had amnesic attacks and it was apparently in one of these that one of the locomotive engineers in our series became responsible for a breach of orders, running past a siding with a resulting collision of his freight with a passenger train. Many of the men were irritable, quarrelsome, inattentive or fuddled. One patient, a locomotive engineer in charge of a very large and powerful engine subsequently described vividly his impulses to run engine, train and all through the terminal station building, and the subsidence of this dangerous irritability following the beginning of treatment. The records of these patients were taken before this study was contemplated, and by another department, so that they are reasonably free from subjective interpretations.

In the effort to ascertain why so large a percentage of serious late syphilis escaped detection in railroad medical examinations, a questionnaire was sent to the medical departments of eight of the largest railroad systems in this country explaining the purpose of the investigation and asking certain questions relating to their methods of examination. The very cordial coöperation of the heads of these departments in replying in detail developed the following facts: All of them require a general physical examination when employees of the types considered enter service. Six of the eight re-examine employees every third year thereafter, and in six the examination is for vision, color sense, and hearing only. Four do Wassermann tests "on suspicion," three do not do them, and only one road has a routine Wassermann test, and that on hospital patients only. Six of the eight make no special effort to recognize syphilis in their employees, two make a special effort, although in one, dining car conductors and waiters apparently receive more than their share of attention because of the directness of their contact with the public rather than because of their responsibility for the safety of trains. Three of the eight medical departments believe there is little syphilis among railroad men and that, what little there is, is not responsible for accidents; three could make no estimate, and two believe the disease to be prevalent and an undetermined menace to public safety. Two roads make routine medical examinations of employees responsible for accidents, five make them on suspicion, and one does not. What should properly constitute suspicion was not defined. Four of the roads urge a more thorough examination for syphilis upon their medical staffs, two contend that

there would be labor union objection, and one feels that only clinical detection of the disease without laboratory tests is practicable.

The situation with reference to syphilis in industrial medical inspection may be summarized in few words. The recognition of syphilis in the personnel of industrial units depends upon the adequate practice of modern clinical medicine. An examination such as the present railroad medical examination, which for any reason fails to detect gross evidence of syphilis in the objective examination of the eye, the heart, and the nervous system, cannot be construed as adequate. It is as much to the interest of the employee to have his syphilis detected before it disables him as it is to the interest of the road or industry to do so before its exchequer, reputation, and earning capacity are endangered by it. The technical demands of such examinations are not beyond the average competent examiner. It is doubly to the interest of the public that both parties to this situation should meet their obligations. The present railroad medical examination could, it seems to us, be improved as follows: First, by the performance of a careful routine Wassermann test on all employees between the ages of 17 and 25, either on entering service or as soon as possible thereafter. The growth of the free State Board of Health laboratory, and its increasing efficiency, might be considered as a means to this end. The Wassermann should be repeated on all men coming to the age of 32. Second, the present railroad medical examination could be improved by annual examination of men between 25 and 40 rather than of men more than 50, if a choice must be made. Such an examination should not be limited to vision, color sense and hearing, ignoring in its narrowness even the pupil of the eye, nor should it limit its consideration of the body to hernia and the results of injury. It should, moreover, invariably call for the fundamentals of a neurologic examination, if possible by a neurologist. The clues derived from it would point the way to special procedures. Third, propaganda for the education of both employees and medical staff to a better appreciation of the importance of syphilis in industrial efficiency and hygiene is in order. One of our brakemen, of his own accord, expressed the wish that his road would send around a car equipped for educational purposes.

Some of the relations of syphilis in railroad employees to the problem of medical diagnosis, to public safety, and to industrial compensation are suggested in the following brief résumés of cases in this series.

**Case 1 (255229).** An engineer in charge of a large superheater developed double vision. In spite of a definite history of infection, and probably because of a negative blood Wassermann, he was told by one physician that he had syphilis, and by another that he did not. He remained on duty until his own mental state alarmed him so much that he gave up his work and voluntarily submitted to a careful examination. He had the typical pupillary and reflex signs of a *tabes dorsalis*, a positive spinal fluid Wassermann test, globulin increased, 46 lymphocytes and a Lange in the indefinite zone. The decline in his irritability and the improvement in his mental state with treatment was striking. He remained at work throughout his treatment and now has a normal spinal fluid.

**Case 2 (253897).** A locomotive engineer, aged 58, continued at work in a progressively bad condition for six months after the onset of definite symptoms. He finally quit voluntarily, and not at the instance of the road, on account of the severity of his dyspnea. On examination he was found to have advanced aortic endocarditis and aortitis, with a positive blood Wassermann test. He also had a duodenal ulcer. Under treatment for his syphilis he made a definite improvement.

**Case 3 (245019).** A railroad brakeman, aged 42, in active service, complained of "rheumatic pains" when lifting, and a recent "strain" acquired while at work. He was on regular duty but of late had grown quarrelsome, was worrying a good deal, and expected to quit. He had been under treatment for syphilis without a complete diagnosis of his condition. On examination he was found to have the clinical, neurologic, and serologic signs of a paresis. His mental condition was such that we advised his physician to make an effort to have him secure other than railroad employment.

**Case 4 (253186).** A railroad brakeman, aged 33, on active duty, came to the clinic because of inguinal hernia. The accidental discovery of a positive Wassermann test on the blood led to a fuller investigation of his case. This disclosed Argyll-Robertson pupils and the early reflex and sensory changes of a *tabes dorsalis*. The spinal fluid was negative.

**Case 5 (264745).** A yardmaster whose last routine medical examination was in 1911, but who had been under the care of railroad physicians for fourteen months, came to the clinic for supposed laryngeal tuberculosis. He had never had a Wassermann test according to his statement. On the finding of a positive test he was placed on treatment and made a remarkably rapid and satisfactory recovery. His history showed that he had developed a mass on the shoulder, probably gummatous, following injury in line of duty, for which he was endeavoring to collect compensation from the road. He had at a previous time received compensation for complications following another injury which suggested the influence of syphilis as a cause of the complication. In addition to the foregoing he had been a continuous source of expense to the railroad for fourteen months during the treatment of a non-existent tuberculosis, only to have the real nature of the trouble identified by a Wassermann test.

**Case 6 (240051).** A yardmaster, aged 47, came to the clinic with retention of urine. It developed that he had been catheterized daily for two weeks in a railroad hospital without a definite diagnosis, although a spinal puncture had been done. Three months before his appearance in the clinic he had been hit on the back by a brake club. No symptoms developed for five weeks, however. On careful inquiry it was found that he had had typical lightning pains and girdle sensations for three or four years, and considerable ataxia in the dark. A neurologic examination showed widely distributed sensory and reflex changes not compatible with a traumatic lesion. The Wassermann test on the blood was negative repeatedly. The spinal fluid was Wassermann negative. Nonne was negative, but the cell count was 6; it later fell to 2 under treatment. At

the end of the first course of treatment retention still persisted but was less in degree. Three months later, after treatment by inunctions, the retention had practically disappeared, the ataxia and lightning pains were gone, and the patient had gained materially in weight.

In the presence of nearly negative serologic findings one hesitates to assign to syphilis the sole etiologic responsibility in this type of case. The neurologic examination, however, suggested the existence of an early cerebrospinal syphilis which probably served as the background of a process initiated or stimulated to activity by the blow on the back received in line of duty. Cases of this type illustrate how subtle may be the influence of obscure luetic infection on ailments and injuries for which workmen may seek compensation.

Case 7 (259815). A railroad conductor on active duty, aged 37, came to the clinic complaining of constipation and a broken nose. The routine general examination at once disclosed the fact that he had unequal pupils inactive to light. On being pressed for a history he admitted a primary lesion in 1905 with some mouth medication and gave a history of shooting pains, attacks of dizziness, and deafness in the left ear. An examination of the spinal fluid showed a negative Wassermann test, a positive globulin test, a pleocytosis of 136 cells, and a gold sol test of 1112232100.

Case 8 (198014). A locomotive engineer, aged 33, came to the clinic complaining of diarrhea. His trouble dated back eighteen months and was believed to have followed the eating of poisoned food at the end of a heavy run. It was not until some time after the onset of diarrhea that his preëxistent cardiac symptoms came to the front. He died eight months after coming under observation, of syphilitic aortitis and myocarditis and secondary damage to the liver and kidneys. He himself believed, and his family insisted, that his condition dated from an accident in line of duty at the time he was struck by the Johnson bar of his engine. An effort was made to secure a statement to this effect to serve as a basis for a compensation claim.

Case 9 (209706). A railroad switchman, aged 31, had developed a squint two years before, for which he had sustained an operation. He had, however, been continued in railroad employ, without investigation of the cause of his squint. It was found that although he came complaining of stomach trouble and rheumatism he had a well-defined tabes dorsalis, although the Wassermann was negative on the blood and spinal fluid. His internal strabismus, probably an early sign of his condition, had apparently received no attention as a sign of syphilis from his physician.

Case 10 (163703). A locomotive engineer, aged 36, at the time of his physical examination in the clinic, complained of difficulty in urination for which a physician had been treating him with sounds on the supposition that he had stricture. On examination he was found to have a positive Wassermann on the blood, and neurologic findings fairly distinctive of tabo-paresis. This patient was under observation and intensive treatment for a period of one and one-half years. He entered on a definite remission and during a period of about six months successfully carried his usual run. Suddenly, however, he returned to the clinic for observation and it developed that he had been "given ninety days" by his superintendent for his responsibility in a freight-passenger wreck. As the patient explained it, one of his "spells" (lapses of memory) had come on him while on the engine and he had passed a siding where his orders were to meet another train. An examination of his spinal fluid at this time showed a rapidly advancing process in his central nervous system apparently unaffected by the treatment he had received. We could find no evidence that the railroad employing this man had made any effort to identify a possible medical factor in his responsibility for the wreck. He was urged to give up railroad work but showed no inclination to do so and disappeared from observation before any further action could be taken.

## SUMMARY

1. A general medical examination of 1763 patients of the Mayo Clinic shows 3.1 per cent of them to have syphilitic infections obvious enough to be detected without the use of the routine Wassermann test. Four and two-tenths per cent of the men and 2.6 per cent of the women have the disease.

2. The lowness of these figures reflects, to some extent, the weakness of clinical judgment in the recognition of this disease as compared with current figures based on the routine Wassermann test.

3. Part of the lowness of these figures is attributable to the large farming element in the clientele of the Clinic and to the low incidence of venereal diseases in the states from which most of the patients are drawn.

4. Of the railroad employees examined 11.7 per cent had syphilis. The disease was eight times as frequent in them as in farmers (1.5 per cent), three times as frequent in them as in business men (3.8 per cent), and twice as frequent as in laborers (6.1 per cent).

5. The doubtful value of the history of infection and the blood Wassermann test in the recognition of these cases is shown by the fact that 24 per cent of the patients gave no history of infection other than gonorrhea; 62.5 per cent had observed no secondary manifestations, and 53 per cent were completely Wassermann negative on the blood.

6. On the other hand, 64 per cent of those whose spinal fluids were examined showed positive findings.

7. Of the diagnoses 58.7 per cent were contributed by laboratory procedures; 41.3 per cent were identified by routine physical examination.

8. Of the men examined 79.5 per cent had syphilis of the nervous system; 18.7 per cent had cardiovascular syphilis.

9. Pupillary abnormalities, muscular paralyses, and fundus changes were present in 62.5 per cent of the cases.

10. Of the patients examined 65.1 per cent showed abnormal knee reflexes and similarly high percentages prevailed for the other simpler details of the neurologic examination. Definite mental symptoms were present in 38.4 per cent.

11. The above findings suggest that the routine railroad medical examination is insufficient to protect the public from the dangers of syphilis in men concerned in the operation of trains.

12. Three suggestions are made with a view to increasing the efficiency of the railroad medical examination with respect to the recognition of syphilis. First, routine Wassermann tests should be performed on all employees between the ages of 17 and 25, by a competent State Board of Health laboratory, and repeated on all employees reaching thirty-two years of age. Second, there should be annual effective examination of men between the ages of 25 and 40 rather than of men over 50. Such examinations should include more attention to pupillary reactions than is at present given, and should employ those fundamentals of the neurologic examination such as tests of the deep reflexes, Romberg, and so forth. These can readily be performed by competent general examiners. Third, formal educational propaganda should be undertaken by railroad medical departments for the education of medical examiners and employees alike to the great significance of syphilis in industrial insufficiency and personal ill health.

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## APPENDIX

In the foregoing study the conclusions involving the characteristics of syphilis in railroad men are based upon a group of 50 patients. Previous experience with statistical groups of 50 based on our records had given us confidence in the accuracy of the results. When the paper was offered for publication, however, the editor of a journal of wide circulation declined it with the seemingly valid criticism that the number of cases was too small to make the deductions of more than minor importance. The authors then undertook to study the accuracy of their own work by carrying out another survey under identically the same conditions as the first. The second group of 50 railroad men like the first was taken at random from our files subsequent to a date after which reasonably complete examinations of all syphilitic patients were made. Every percentage estimate incorporated in the preceding paper was checked against the results in the second survey. The very striking parallelism of the results is apparent in Table 5 and will serve, we believe, as a confirmation of the accuracy of this type of work. By way of a critique on the belief that vast numbers of cases are essential to accurate conclusions in modern medicine we submit the contention that the accuracy and completeness of the study of the individual cases made possible by modern diagnostic method renders the indefinite multiplication of numbers of cases unnecessary. The purpose of numbers is to eliminate the inexactitudes inseparable from primitive work and unchecked observation. For every inexactitude which can be replaced by an exactitude the number of cases necessary to illustrate a point diminishes roughly in proportion to the increased accuracy afforded by the new test or method. While the diagnosis of syphilis has not by any means as yet been reduced to a mathematical problem it is a pleasure to find that searching and painstaking study of a small group of cases by all known methods seems to yield results whose accuracy is equal if not superior to those of large series of cases subjected to less intensive investigation.

TABLE 5.—COMPARISON OF DUPLICATE SURVEYS OF TWO GROUPS OF FIFTY RAILROAD MEN EACH. THE PRECEDING ARTICLE WAS BASED ON THE FIRST GROUP.

GENERAL DATA		
	First series per cent	Second series per cent
Cerebrospinal fluid positive.....	64	79
Lues, central nervous system.....	79.5	83
Lues III, cardiovascular.....	18.7	20
Blood Wassermann negative.....	57	58
Blood Wassermann positive.....	43	42
Wassermann weak positive.....	4	2
Use of alcohol.....	75	61
Heavy drinkers.....	36	33
History of lues II unobtainable.....	62.5	60
Lues recognized at some time.....	55	57
Age of onset late symptoms—over 30.....	78	75
Gonorrheal history positive.....	80	73
Gonorrhea only.....	24	19
Symptoms appearing from six to twenty years after infection.....	71	67
Per cent infected, by the age of 32.....	91	81
Wassermann on men under 25 will reach.....	70	60
Sterile or pathologic marriages.....	44	50
Age on entry—patients between 35 and 40.....	32	36
Concerned in operation of trains.....	76	70
Concerned in operation of engines.....	36	36
SYMPTOMATOLOGY		
Gastric.....	28	22
Not suggestive of lues.....	18	24
Headaches and head pains.....	16	16
Cardiac.....	14	16
Diplopia and poor vision.....	14	10
Malaise, weakness.....	12	8
Shooting pains.....	10	20
Bladder (subjective).....	10	4
Nervousness.....	8	
"Do I have syphilis?".....	8	6
Laryngeal.....	8	6
"Rheumatism".....	4	18
Ataxia (subjective).....	4	6
Girdle pain.....	4	4
Dizziness.....	2	8
OBJECTIVE EXAMINATION		
Abnormal knee reflexes.....	65.1	79
Abnormal Achilles.....	78.1	62
Romberg positive.....	38	42
Speech defect.....	15.7	17
Mental symptoms.....	38.4	38
Paresthesias.....	55.8	51.3
Ataxia (objective).....	36.8	36.3
Bladder (objective).....	47.5	20.5

## THE NEED OF HOSPITAL BEDS FOR SYPHILIS

### General Aspects of the Hospital Problem of Syphilis: Contributions the General Hospital Should Make to Management and Care of the Disease: Bed Requirements of the Work.

J. H. STOKES

The problem of the care of syphilis is rapidly passing from obscurity into the limelight of a public health issue. Thanks to the vigorous backing of federal and state governments, the time will soon be past when it will be either expedient or possible for anyone engaged in an activity involving the care of the sick to ignore the issue or refuse to make provision for it. Realizing the recent rapid change in point of view toward such questions, the American Hospital Association is urging institutions all over the country to take an active interest in the care of genital infections and to coöperate with the federal program in developing appropriate facilities. The question at once arises as to what are appropriate facilities and what part the hospitals of the country shall play in supplying them; and it is with a view to contributing something as an answer to this question that the director of the Boston Dispensary has asked me to discuss the need of hospital facilities for the care of syphilis.

On several previous occasions<sup>1</sup> I have attempted to outline general aspects of the hospital problem of syphilis. The existence of such a problem is now well established, and its importance can be inferred from the very large part hospitals play in the national program of Great Britain, as developed by the Sydenham Royal Commission and placed in actual operation by the British local government boards. It is noteworthy that responsibility in this remarkably conservative and yet complete program is squarely placed, not upon special venereal or segregated hospitals, of which the commission expressly disapproves, but upon the general hospitals of Great Britain. Syphilis is a problem for the general hospital which already treats the condition all the

Reprinted from *Mod. Hosp.* 1919, xii, 390-392.

time under one disguise or another, scattering its various manifestations through perhaps acres of wards and a multiplicity of services, and either ignoring its existence or employing a variety of therapeutic methods second in number and variety only to the number and variety of the patients themselves. It has never really been a question with the general hospital whether it would permit the importation of the disease into its precincts, since such importation, often in the most contagious because least recognized form, is a constant element in all hospital work.

The best available evidence of the extent of the hospital problem of syphilis is contained in Wassermann surveys upon groups of in-patients on various large representative services in this country.\* Estimates of its prevalence in hospital populations range from 6 to 25 per cent, depending, of course, to no small extent upon the types of patients dealt with, and involving also a certain element of inaccuracy inseparable from the shortcomings of the Wassermann test as a means of identifying syphilis. It may be taken, however, that a range of from 6 to 10 per cent of all patients admitted is conservative for the average hospital. More, rather than less, syphilis will probably be identified in hospital populations, as other aids, including expert syphilologic and spinal fluid examinations, are invoked.

Since the figures given deal with the bed services of hospitals, they are apropos in a consideration of the duty of a hospital to provide beds for syphilis. The estimates quoted demonstrate, by the very fact that the patients included in them occupy beds, the fact that there is such a thing as a bed problem in the management of syphilis. The ambula-

\* Positive Wassermann tests in patients on various hospital services revealed the followings percentages of syphilis:

23 per cent of 101 children examined at the Children's Memorial Hospital, Chicago,  
31 per cent of 111 children admitted to the Children's Hospital, Boston (Lucas, W. P.: *Boston Med. and Surg. Jour.*, 1913, clxix, 423-424.)

24.7 per cent of 312 cases, Boston Marine Hospital. (*Public Health Reports* No. 27, Cited in *Jour. Am. Med. Assn.*, 1916, lxvii, 1821.)

15 per cent of 4,000 hospital patients Peter Bent Brigham Hospital (Walker, I. C. and Haller, D. A.: *Jour. Am. Med. Assn.*, 1916, lxvi, 488-491.)

16 per cent of 500 patients, Boston City Hospital. (Hornor, A. A.: *Boston Med. and Surg. Jour.*, 1916, clxxiv, 194-195.)

11.3 per cent of 160 pregnant women, Cook County Hospital, Chicago. (Falls, F. T. and Moore, J. J.: *Jour. Am. Med. Assn.*, 1916, lxvii, 574-579).

6 per cent of 2,000 patients in the gynecological service of the University Hospital, Ann Arbor, Michigan. (Peterson, R.: *Surg. Gynec. and Obst.*, 1916, xiii, 280-283.)

tory conception of the disease has unfortunately in this country overshadowed the appreciation of the very just claim of this most serious infection to adequate provision for its victims in the wards and rooms of hospitals. Since I have discussed them elsewhere, I merely summarize here categorically the eight ways in which the general hospital should contribute to the management of syphilis and derive reciprocal benefit from the relation.

1. Syphilis is often recognized by the hospital serologist when no other signs present themselves. The hospital serologist, by reason of training and environment, is especially fitted to be the performer of an authentic and trustworthy Wassermann, which is badly needed in these days. Of 500 patients examined by Hornor (Boston City Hospital), 16 per cent had syphilis, although 2 per cent had been identified by other means than the Wassermann.

2. Syphilis needs, for the proper care of its medical, surgical, neurologic and special complications, the prolonged observation, coöperative diagnosis, and control which only a stable, well-organized hospital service can supply.

3. The actual technic of the intensive treatment of syphilis requires beds. Therapeutic control, a low mortality, and the successful management of the very sick patient, which is much commoner in syphilis than is generally realized, all demand something more than ambulatory facilities.

4. The hospital bed service is needed for a brief but necessary quarantine, which can be carried out without the slightest risk to other patients or the medical and nursing staff.

5. Well-organized treatment for syphilis, such as a hospital service can provide, has the same value in syphilis as sanatorium care has in tuberculosis. It is a factor in inculcating a sense of social responsibility in the patient and in encouraging ideals of rehabilitation and cure.

6. Organized hospital care of syphilis provide centers for the follow-up control so essential in the disease, for the development of the record systems, and for the outside professional coöperation essential to adequate treatment.

7. The hospital service provides the only place in which syphilis can be made a subject of thorough study and research.

8. The existence of a specially organized service for syphilis is of material assistance to any hospital group of diagnosticians in the

prevention of blunders which arise from overlooking syphilis as a factor in diagnosis, and in the protection of staff and patients from the dangers attendant upon the admission of unrecognized contagious cases to wards and operating rooms without adequate supervision.

On each of these points it is possible for any active syphilologic service to supply an abundance of concrete evidence. I have seen three extragenital infections in one year in the surgical personnel of a five-hundred-bed hospital, all of which could have been prevented had there been adequate diagnosis of syphilis. The diagnostic blunders of a staff which lacks a syphilologist and a syphilologic service to put an edge on the recognition of the disease are often serious, but are properly the subject of a medical rather than a general presentation. Emphasis should be placed on the need of beds for intensive treatment. The administration of arsphenamin has enough complications and enough serious effects, direct and indirect, to justify the same period of hospital observation as a tonsillectomy. The really intensive treatment of syphilis, if carried out by a dispensary, must either subject the patient to unreasonable risk or sacrifice effectiveness by reductions in dosage and loss of therapeutic control.

#### THE BED REQUIREMENTS OF SYPHILOLOGIC WORK

How many beds are needed to meet the requirements of a service for syphilis? To show the inadequacy of existing provision, in general, the authoritative estimate of Pontoppidan, based on a very large Danish experience, should be recalled. For all the genital infections, there should be an average provision of one bed for each 2000 population. The existing situation in large cities more nearly approaches one bed to 10,000 population. As directly applicable to hospital and group practice, my own study of this question with respect to syphilis has led me to suggest the following basis for estimates: The number of beds required for syphilis will vary with the type of hospital and with its clientele, but it is conservative to estimate that the average hospital will be called upon to deal with at least a 6 per cent proportion of syphilis among its patients. Time is a factor in the number of beds required. Where 5 patients are confined to hospital six weeks apiece, they occupy as much per annum bed space as 30 patients who stay only one week. Under a properly organized system, the "turn-over" of average syphilis in a hospital can be rapid and can, in my experience, be reduced to about seven days of hospital residence per patient, per course. If courses are repeated

it will be necessary to regard the returning patient as a new patient in estimating the bed capacity required.

On the 6 per cent basis, a general hospital receiving 7,000 patients annually will admit about 500 patients with syphilis, who, on a basis of one week's stay, will maintain a service of ten beds. As a matter of fact, the percentage of "sick" syphilis admitted to a general hospital may be higher and turn-over will be delayed, so that the bed requirement will probably be nearer fifteen than ten beds. In my experience with various hospital services for syphilis these estimates seem to work out well in practice. For a service seeing 1,500 syphilitics annually, thirty beds in none too large an allotment. On the service of the Section of Dermatology and Syphilology of the Mayo Clinic, treating from 1,500 to 1,800 syphilitics per annum, thirty beds exclusively for syphilis are proving inadequate to the requirements. The majority of these patients are treated on the basis of six hospital days apiece, per course. In such a service, combining dermatology and syphilis, so that practically all aspects of the latter disease from the earliest to the latest stages are represented, 3,600 to 4,000 patients a year require fifty to sixty beds in order that proper care may be given to every type of case. The 2000 syphilitics in such a service require about thirty-five to forty of the beds.

The care of syphilis under any circumstances embraces an ambulatory as well as a hospital phase. The former is represented in a way by the consultant's offices, as in the Mayo Clinic, or by the dispensary. The latter centers in the hospital. To achieve maximum harmony and efficiency, in- and out-patient phases must be under the same chief and the same staff. This fusion of office and hospital work into one is spoken of elsewhere as "unit organization." Every service for syphilis must choose its clientele within fairly well-defined limits. Free service and night clinics attract a certain group and repel another. Coördinated, organized, large-scale pay service, as in a group practice, is attractive and acceptable to another large body of patients, but repels those who demand and can pay for the exclusive attention of a specialist, though the latter may be medically the less efficient of the two. The success of any service for syphilis will be proportional to the extent to which it individualizes its patients, and the amount of individualization necessary will increase proportionally to the social status of the clientele. In a public service, with its stalls and booths, its line-up and publicity, individualization is at its lowest. In the pay clientele of a large group practice the extent to which individuali-

zation and special consideration for the patient can be carried will determine, in the last analysis, the drawing power, the influence, and the patronage of the service. To secure such intensive individualization, unit organization is a *sine qua non*.

The importance of certain of the principles enunciated in this article has been abundantly borne out by my experience in the development of the work of the Section of Dermatology and Syphilology of the Mayo Clinic. The single-room type of hospital construction, a mechanical aid to individualization, is the type toward which we are striving. A special atmosphere can and should be created, akin in many of its qualities to the atmosphere of the best types of tuberculosis sanatoriums. Line-ups, publicity, crudity, rough-and-ready methods, noise and lack of refinement, coldness and lack of good will, are all dangerous to the integrity and success of any special service for this disease which deals with the so-called great middle class. Nor is there any reason why the poor should be obliged to submit to them merely because of their poverty. High-grade nursing, exceptional tact and discretion, the qualities of mind and heart in the staff which keep the patient always affectionately reminded of the department, are business assets in the care of syphilis no less than in the sale of goods and the building of commercial success.

The methods and principles described have, it is believed, no merely local applicability. They may be adapted to many types of hospitals and a variety of conditions. Organization can not, however, be carried out on theory alone. Nothing can be expected in the way of results where managerial niggardliness denies a newly organized service the sinews of war in the form of such equipment in offices and hospital beds as its performance can justify. Equally little can be expected where professional distrust and medical penny politics block the access to the legitimate field of the syphilologist. If a liberal policy and generous coöperation from co-workers prevail, an enthusiast with a little judgment, using material that now lies ready at hand, can quickly show, even with the most unassuming beginnings, that in the field of hospital care for the syphilitic there are possibilities for reward and humanitarian service that have lain too long untouched.

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## **HEAD, TRUNK AND EXTREMITIES**



## THE TREATMENT OF TUBERCULOSIS OF THE SPINE\*

H. W. MEYERDING

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Early diagnosis and careful prolonged care of the patient under competent supervision are essential in order to obtain favorable results when tuberculosis attacks the spine. Although conservative treatment has given a fair percentage of favorable results, a definite group remains in which the surgical fusions of Hibbs and Albee have shortened the period of disability, prevented further deformity, and given more certain relief than conservative measures, thus placing these operations on a sound surgical foundation in the armamentarium of treatment.

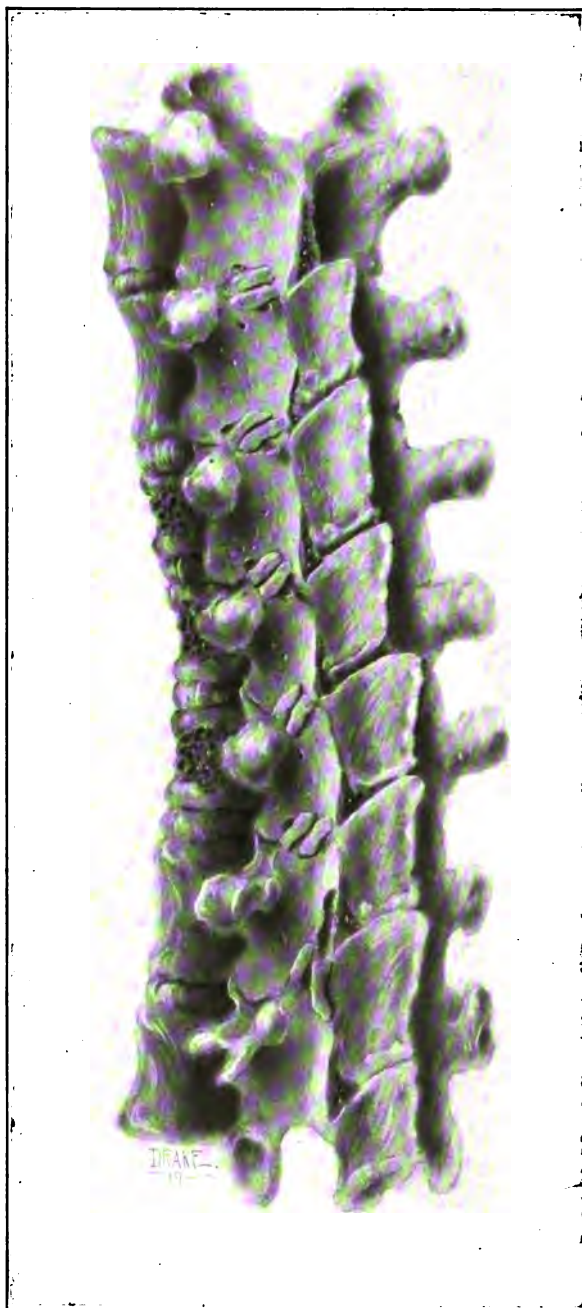
The fact that the spinous processes and laminæ are seldom involved in tuberculous spondylitis makes the fusion operations practical. It is to be remembered, however, that the disease process is merely immobilized by such surgery and the deformity remains, that the patient is tuberculous, and that a focus in another part of the body probably exists. Nature is slow in producing ankylosis, and external splinting to immobilize completely is impossible; surgery, on the other hand, gives the best fixation in a comparatively short time.

Hibbs has reported (1916-1918) excellent results from his subperiosteal fusion. He believes that all patients who will take anesthesia should be operated on. He constructs a periosteal tube filled with the fractured spinous processes and the freshened ends of the laminæ from which spiculæ of bone are chiseled and bridged; he has practically always produced fusion (Fig. 285).

Albee credits his bone grafting operation, which consists of removing a long section of bone, preferably from the tibia, and placing it in the split spinous processes so as to bridge the diseased area well above and below, with 85.25 per cent results following 539 operations

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**FIG. 1.—Hibbs operation. Fractured spinous process and spiculæ of bone bridging freshened edges of laminæ.**

collected from various clinics. The disease was arrested in 460, improved in 59, and unimproved in 20 (Fig. 286).

Of 405 patients with Pott's disease observed at the Mayo Clinic from September, 1912 to January, 1918, 100 were operated on by a modified Albee bone grafting method.

Age

9	were patients between	1 and 10 years
5	were patients between	11 and 20 years
56	were patients between	21 and 30 years
19	were patients between	31 and 40 years
7	were patients between	41 and 50 years
4	were patients between	51 and 60 years
Average age of the patients,		25 years

Sixty-five per cent were males and 35 per cent females. Eight patients had had symptoms less than one year; 24 had had symptoms for from one to two years; 21 for from two to three years; 13 for from three to four years; and 10 for from four to five years; one patient had had symptoms for nineteen years.

Twenty-two gave a history of trauma to the area involved; 78 did not mention an injury. Twenty-seven had had tuberculosis in other organs, lungs, joints, testicles, peritoneum, and so forth, before symptoms were manifested in the spine. Symptoms of paraplegia were present in 7 and were not considered contraindication to operation.

The disease was located in the high dorsal region in 2 patients; middorsal in 14; low dorsal in 27; dorso-lumbar in 11, and lumbar in 46. Definite abscesses existed in 8 patients, suppurating sinuses in 9, and deformity in 78. Previous treatment had been unsatisfactory and had consisted of the application of casts and braces, and in 3 of the cases bone grafting had been done elsewhere.

In all instances a thorough clinical examination should be made with special attention to locating the primary focus. The x-ray is indispensable in determining the extent of the disease, and the amount of calcification, and frequently it demonstrates abscess formation and old healed tuberculous pulmonary lesions, otherwise difficult to diagnose. While Pott's disease may usually be diagnosed without difficulty, the x-ray is of great value in the differential diagnosis. The von Pirquet test serves a limited field in the very young and its value decreases with advancing age. Blood count, temperature, and so forth,

aid in giving clues to anemia, secondary infection, and the activity of the disease.

It has been our experience that the most favorable results are to be obtained by a proper selection of patients to be operated on and the continuance of the conservative treatment after operation until,

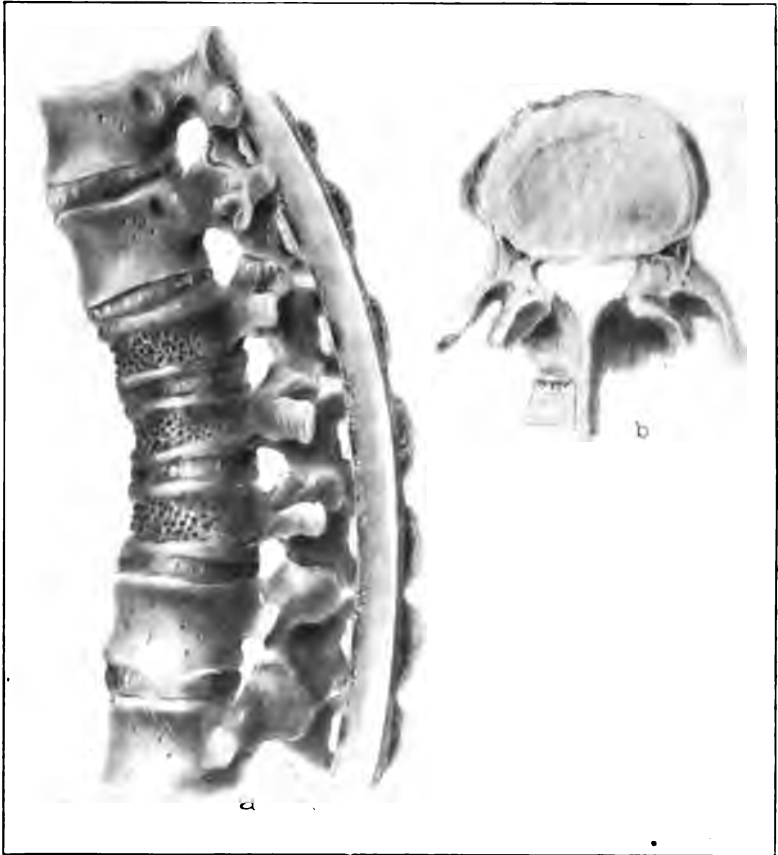


FIG. 286.—a, Modified Albee operation; lateral view shows a curved graft placed so as to bridge two vertebrae above and two below the tuberculous lesion; b, superior view shows graft in position.

in the judgment of the surgeon, the disease process has been arrested. The bone graft used in our cases was curved to fit the deformity (Fig. 287). The very young and those adult patients who present formidable complications are treated conservatively. Recumbency, rest, and general physical hygiene are essential in all cases. Patients under 5 and adults who present complications, such as suppurating

sinuses and pulmonary tuberculosis, should be treated by means of the Bradford frame for a period usually from six months to one year, or until the disease has been arrested. This is followed by plaster of Paris casts applied so as to take off the weight-bearing from the diseased area



FIG. 287.—*a*, Incision in the skin to expose the flat internal surface of the tibia. The dotted line represents outline of curved bone graft removed by bone saw; *b*, cross section of tibia showing the shape and comparative size of graft.

and give the spine as much fixation in extension as is possible (Fig. 288). Still later a Taylor spinal brace is applied. In some instances when the general condition has improved, but the symptoms of spinal disease remain unarrested after such treatment, bone graft operation may be



resorted to with benefit and the braces afterward removed. The Calot jacket and suspension jury masts are useful, especially when the disease attacks the upper dorsal and cervical spine. When the jacket is properly applied it will give beneficial fixation (Fig. 289). Many patients have been treated by cast and brace which fail to support the weight above the diseased area. The result of the application of such apparatus is more harmful than beneficial, since it acts as a restrictor of respiration and adds to the weight and discomfort of the



FIG. 288.—Support for surgical Pott's disease consisting of steel bands reinforced by leather, plaster paris or celluloid.

already overburdened body. A properly applied jacket allows breathing space, it hyperextends the spine, and supports the weight above the necrosed area. All braces should be applied under the supervision of the attending surgeon and never left to the bracemaker, for, while the latter may be proficient in the making of the brace, the principle and adjustment require a knowledge of the extent of the disease itself.

What has been said of the cast and its application may be said also of the brace. Many are positively harmful. Recumbency without doubt is the most satisfactory aid to treatment. When early diagnosis is made, and fusion is induced surgically, reinforced later by some means of external fixation, and general antituberculosis treatment is adopted, marked deformity and complication will soon become rare.

Tuberculosis when healed by nature most often leaves the unfortunate a cripple, perhaps with draining sinuses, and not uncommonly, paralyzed. The Rollier sunshine treatment should be urged, and it should be instituted while the patient is under control. Medication may be indicated when anemia of a secondary nature is present but in many instances good nourishing diet, cod liver oil, and fresh air and sunshine meet all the requirements. Inasmuch as the lesion in the spine is a local manifestation of a disease process which has probably had its origin in a primary focus in some other part of the body, the general hygienic care of the patient is of first importance. A rule with regard

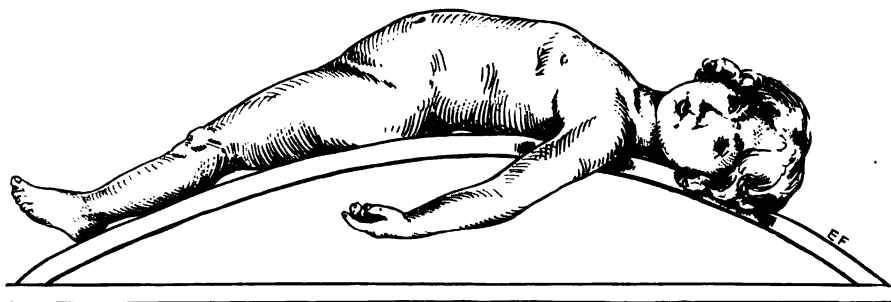


FIG. 289.—Bradford frame showing hyperextension obtained.

to the period of recumbency would be impractical, especially in conservative treatment, since the conditions as to activity, extent, and abscess complications vary so much at the time the patients present themselves for treatment.

It is somewhat difficult to decide when the patient should be allowed to get up after operation, and the judgment of the surgeons varies in different clinics. Usually the patient's relief and desire to move is of value, and when his temperature is normal and he is free from pain and muscle spasm, he may be given permission to sit up after a properly fitted brace has been applied. Later an x-ray is taken; the amount of calcification and union found are of importance in determining the extent of repair. At the clinic the period of recumbency and the time on the Bradford frame are determined by the condition of the patient after repeated examinations; no definite time for conservative treatment is established. After the period of recumbency a cast is applied, and still later a spinal brace. All the while the patient and his relatives are impressed with the value of the general

care, especially the fresh air and sunshine (Rollier). All patients treated by recumbency should be kept in an institution long enough to instruct the parents or other relatives with the method; in this way much better results are obtainable and the parent who is alarmed on seeing the child on the frame for the first time will later become a firm believer in the value of the method. The great danger is in the first week when the child cries and the parent desires to hold or rock the child, thus halting or breaking up the treatment. A child with tuberculosis of the spine almost never cries to get off the frame when once its back has become accustomed to the new position and the pain is relieved.

While the time of recumbency cannot definitely be given, a year will usually suffice, especially if hyperextension and heliotherapy are combined with fresh air, and proper food and nursing. In surgical cases the time of recumbency is lessened; in most of our cases the patient is up and about in six weeks with a cast or brace. Care must be taken not to fracture or loosen the graft, since during recumbency and when the patient is turned, as well as when he is up and about, the spine must be kept from rotation and flexion. Nurses are taught to turn the patient by rolling, the shoulder and thigh being grasped so as to prevent twisting of the spine. A well fitted cast, split before operation and padded and re-applied immediately after, is the best method of fixation in bed. A stiff bed should be used, however, and the spring reinforced with transverse boards. During the sixth week the brace is applied while the patient is in bed; he is allowed to become accustomed to the upright position on a back rest and later to sit in a chair. Within the next few days the patient in most instances begins walking and is then cautioned against removing the brace unless he is recumbent.

It is obvious that the reported results vary according to the interpretation of cure. It is considered desirable to express value of treatment in terms of improved and unimproved conditions. If the patient is relieved of pain and is able to return to activity, although the deformity and even evidence of psoas abscess remain he should be considered as benefited by operation and is so reported in this series. All patients are advised against heavy manual labor, but some have returned to farming and one to the occupation of lineman, which required climbing telephone poles. Eighty-six per cent of the patients in the series have been relieved of clinical symptoms. Three patients

are unimproved; 3 have not been heard from. Eight patients have died since operation: (1) One child aged 4 who had had symptoms for two years, and presented a kyphos was operated on and recovered sufficiently to attend school. Death was reported eighteen months after operation, due to tuberculous meningitis. (2) A woman aged 26, who had had symptoms five years, died twenty-two months after operation of tuberculous peritonitis. The post-mortem examination showed the graft ankylosed and the spine healed. (3) The death was reported of a man aged 51 who had had symptoms for two years, but no cause or date was given. (4) A woman aged 26 died from tuberculous peritonitis. She had been dismissed with a brace, apparently improved. (5) One man aged 35 had had symptoms three years. He died from miliary tuberculosis; tuberculous adrenals, and tuberculous spine. (6) A man aged 24 with symptoms of eighteen months' duration died six months after operation; the cause is not known. A psoas abscess was present at the time of operation. (7) A man aged 24 with six years of symptoms died of pulmonary embolism the twelfth day after operation while still recumbent and as he was reaching out for a book. (8) A man aged 39 whose condition was complicated by an old pulmonary tuberculosis, and who had had spinal symptoms one year, died of meningitis thirteen days after operation; the cause of death was tuberculous meningitis.

#### SUMMARY

1. The fusion operations of Hibbs and Albee for tuberculosis of the spine have given a means of internal fixation which shortens recumbency, prevents further deformity, and tends to hasten the healing of the diseased process.

2. The diseased process in the vertebral bodies is not eradicated by the fusion operations and relief of symptoms does not mean cure of the disease.

3. The value of general anti-tuberculous measures is of primary importance and should be insisted on.

4. Recumbency and external fixation are still necessary adjuncts to successful treatment and should be carefully carried out.

5. Abscesses should be let alone unless they cause discomfort or pain, or are secondarily infected, when they should then be carefully aspirated and injected.

6. A primary focus which may be determined in a small number of cases indicates a general disease of which the spinal symptoms are manifestations.

7. Children under 5 and adults with active pulmonary lesions and sinuses are poor risks.

8. Paraplegia does not contraindicate operation for fixation.

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## INTRACAPSULAR EXTRACTION OF CATARACTS\*

W. L. BENEDICT

Practically all ophthalmologists admit the advantages of the intracapsular extraction of senile cataract; the operation is being practiced as the best method of extraction of cataractous lenses of certain types. The comparative freedom from iritis and the long periods of reaction during the absorption of retained cortical material is enough in itself to make the intracapsular method appeal to the operator, and the elimination of the possibility of after-cataract certainly is a source of great satisfaction to both the operator and the patient. Days and weeks of time are saved in the convalescence; within a few days the patient can return to work with good vision and with visual acuity that will improve with time instead of becoming less acute. The method is a distinct advantage to elderly persons with whom time may be a factor of great importance. Protracted convalescence in a hospital often precipitates a mental depression from which these old people never recover. The physical infirmities they have heretofore hopefully and cheerfully mastered now become manifest and dominant, so that even with improvement in vision they sometimes leave the hospital more helpless than when they entered. While as a rule elderly persons make good patients it is better to confine them to bed as little as possible, and to get them into their homes or into a home-like environment with little delay.

The greater part of postoperative complications arises from retention of lens matter in the chamber, or from delayed closure of the wound because of incarcerated shreds of capsule. It is to the marked advantage of the intracapsular method of extraction that these complications are very much reduced in frequency. Statistics show that the intracapsular method has a smaller percentage of prolapse of vitreous, prolapse of iris, iritis, and total loss than other methods of

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extraction, and an equal percentage of incarceration of iris, with no discission and no suppuration.

The development of intracapsular operations forms an interesting chapter in ophthalmology and should be reviewed by every surgeon who attempts cataract operations. For many years attempts have been made to perfect a method of extraction which would not leave a corneal scar, which would leave a round black pupil with no capsular nor other debris to obstruct the light. The extraction of the cataract in the capsule was first introduced by Pagenstecher in September, 1863 as a routine operation for senile cataract (Würdemann). His method was to incise the cornea in the ordinary manner, to perform an iridectomy, and, after entering the spoon behind the lens, to exert pressure on the cornea through the lower lid. Quite as frequently he tried to express the lens by pressure without introducing the spoon, reserving the use of that instrument for cases in which the lens did not readily deliver. He selected patients whose cataracts were hard or hypermature and whom he thought could be kept under control. His vitreous loss is given as 53 per cent.

Modifications of the Pagenstecher operation have been brought out from time to time, advocated, and passed into disuse. The extracapsular method of extraction, as practiced by von Graefe, became the method of choice for most surgeons, and for several years the operation was believed to be standardized. Accidents and complications had been considered reduced to a statistical minimum, that is, losses were assumed to be about 4 per cent in the hands of good operators, and discission of after-cataract was believed to be necessary in from 40 to 60 per cent of cases. The danger of total loss or violent reaction following discission of the after-cataract had been considered liabilities which the patient had to accept; often more than one discission was necessary. Pioneer work in developing new methods of extraction was undertaken by only a few and condemned by most as subjecting the patient to unfair risk. Why should one deviate from an operation, that one understands thoroughly to accept a new one admittedly harder to perform and in which danger of loss of sight from complication lurks in unknown and unsuspected places? Enough of the unpleasant happenings accompanying early attempts at intracapsular extraction were known to the masters of the von Graefe and other extracapsular methods to make them very cautious not only in operating but also in accepting the statement of good results achieved

by those who from time to time reported cases operated on by the new method. Indeed there was little in these early reports to induce one to take up the method described. It remained for Smith to move the world by his stupendous mass of data and his insistence that he had devised an entirely new method of extraction to shake the conviction of the conservative ophthalmologist that the intracapsular method of extraction is unsafe. By many of our American and British surgeons the method as described was attacked as cruel, brutal, inhuman, unreasonable, and unoriginal. The only thing new about it seemed to be the high percentage of good results reported in a series of cases much larger than that of any other surgeon. To be sure it seemed wonderful, unbelievable, yet the logic of intracapsular extraction went home. That removal of the capsule with the lens is ideal if it can be done without too great risk had to be accepted. We were perfectly willing to admit that the greatest satisfaction and the least uneasiness were experienced when the eye was left clearly rid of all substance that might set up reaction, and that better visual results could be expected. The Smith-Indian operation was difficult to perform, however, it was better suited to the unintelligent, unemotional, easily satisfied nature of the Jullundur who could not read anyway, than to the exacting demands of people of the temperate zones of Europe and America. Then, too, there was little encouragement in the statement of the originator that "the operators outside of India who have not had a special course of training in the manipulative art connected with it, or the operator who has not had such training and whose experience is limited to a hundred cataracts a year or less, will be well advised to avoid this operation."

Very few American operators were doing more than 100 extractions a year, yet this did not deter a few from training with the master and bringing to our people the advantages obtained by his operation. His pupils, realizing the differences in patients and hospital conditions, were quick to improvise ways to meet the principal objections to his operation, and, so far as I know, no American ophthalmologist is consistently practicing the Smith-Indian extraction in all its details as laid down by Smith. Every detail from cleansing the culdesac to the after-care of the patient is claimed by Smith as of his own devising and in all fairness to him should be rigidly followed in cases purported to be done by his method. That it is not followed so consistently is not to the discredit of Smith himself, or to the theory



of intracapsular extraction, but to the credit of American surgeons who are ever active in the best interests of their patients and quick to take up that which is proved to be good. The problems of lid retractors, preliminary preparation of the eye, and the first steps of the operation itself were gradually worked out. Lack of an experienced assistant to hold the lids has been met by mechanical retractors and hooks. Irrigation of the conjunctival culdesac with strong solutions of mercury salts has been found to be harmless and efficient.

Smith advocated a section ending within the cornea, but the limbal section upward with a small conjunctival flap has held its own place as first choice with most surgeons. The section should include a little less than half the circumference of the cornea, and the flap should begin with the section. Better and quicker union is obtained in this manner. "So uniform is the consensus of opinion upon the formation of the section and conjunctival flap that it would not repay us to spend time now on the consideration of details of relatively slight importance" (Parsons).

The question of iridectomy seems to have been settled by Smith's abandonment of the simple extraction and adoption of the iridectomy as a routine procedure. In 1912 Stanculeanu modified his operation by omitting the homotropin instillation and substituting iridectomy (Hansell). In simple extraction prolapse of the iris is a not infrequent complication that is difficult to deal with and that frequently necessitates an iridectomy or iridotomy later. The question of whether the iridectomy should be done before or after the extraction may be left to the individual surgeon. Its function is the same, namely, to lessen the danger of prolapse of the iris and to lessen the probability of subsequent glaucoma by a free interchange of fluid between the two chambers.

Attempts to devise safer methods of extraction of the lens in the capsule have given rise to the wide variation in technic found in present use. In one of the two earlier methods employed, a spoon or scoop was introduced into the vitreous and under the lens to lift the lens up against the cornea; then, by use of a spoon, pressure was applied to the cornea below the lens border and the lens was skidded through the wound. In the second method, without introducing any instrument into the eye, pressure was applied through the lower lid or directly on the globe at the lower border of the cornea, counter pressure being applied above the wound when the lens did not deliver

readily or when the vitreous prolapse was unduly large. During the next few years special instruments were devised to remove the lens by pressure or by traction, or by a combination of these two methods. Among these may be mentioned the cystotome, hook, vectis, "detacher," reclinateur, spoons, glass rods, and vacuum extractor.

The Smith-Indian method was by pressure applied to the outside of the globe. Objections to this method, which seem to have been well sustained, are abrasion of corneal epithelium, vitreous coming out at the side before the lens is delivered, and prolapse of the iris. The latter objection was removed by doing an iridectomy. The abrasion of corneal epithelium has been reduced by the use of a delivery hook with rounded side and blunt end, but injury to the posterior corneal epithelium causing striped keratitis still remains a factor in delaying visual acuity in cases in which considerable buckling of the cornea is necessary to express the lens. Injury to the cornea was reduced by first dislocating the lens by use of a reclinateur, and vitreous loss was made much less probable by requiring less pressure than that necessary to rupture the zonula and by the use of improved lid retractors.

In 1910 Knapp began the use of the Kalt forceps to dislocate the cataractous lens, after which he expressed it by the Smith-Indian method. A year later Stanculeanu reported a method of extraction which, after the usual section and iridectomy, was characterized by grasping the anterior capsule of the lens by means of a capsule forceps made without teeth, and designed to hold the capsule without tearing it. The lens was moved from side to side and up and down, thereby rupturing the zonular attachment. The forceps was then removed and the lens delivered by pressure on the globe by the use of a spoon.

Török noticed the firm grip taken on the capsule by the Kalt forceps and how easily the zonular attachments can be ruptured with it. He stated that if capsule forceps instead of a cystotome is used, often a hypermature cataract with thickened capsule does not rupture, but the zonula gives way and the lens is delivered in the capsule. He imitated this accidental delivery in the capsule by aiding in the rupturing of the zonula by applying intermittent pressure on the globe below the cornea by means of a Daviel spoon simultaneous with side to side movements with the forceps. As soon as the zonula ruptured, the pressure on the cornea became continuous and followed the lens, as in the von Graefe extraction, and the lens was delivered with its lower edge first. There was a loss of vitreous in only two of 37 successful extractions.

## TECHNIC OF OPERATION

The Kalt forceps was recommended to me as being well adapted for the removal of the anterior capsule in performing the usual extracapsular extraction, and I began to use it for that purpose. In a few instances the lens became luxated and I expressed it in the capsule with a Daviel spoon after the usual manner. There was no loss of vitreous and the eye healed without incident within a very few days. I then attempted the extraction of the lens in the capsule in selected cases, grasping the capsule with the forceps and making traction as well as side-to-side movements; I was often successful in pulling the intact lens through the incision without applying pressure to the globe. However, quite as frequently the capsule ruptured before the zonula gave way or as the lens was being delivered; this delivery could not be classed as an intracapsular extraction. I found that the zonula could be ruptured more easily by applying pressure below the lens by means of a Daviel spoon after the grasp of the capsule was secured than by means of side-to-side movements with the forceps. Furthermore, it was evident that the lens could be raised slightly to engage in the wound even before the zonula gave way, thereby preventing the escape of vitreous around the side of the lens. Traction upward or toward the wound was combined, therefore, simultaneously with the pressure on the globe below, care being exercised not to exert sufficient traction on the capsule to rupture it. When the zonula gave way the lens immediately engaged in the wound without turning or "tumbling." Pressure with the Daviel spoon was now made to follow the lens as described by Török until the lens was slightly more than half through; the pressure was then discontinued entirely. From this point the lens was removed by the use of the forceps alone; thus there was no pressure on the globe after the resistance to pressure was removed by birth of the lens. The iris pillars were then replaced, the conjunctival flap adjusted, and the eye closed in the usual manner.

Soon it became evident that some types of cataract are not well suited to this method of extraction. In general these fall into the classes that have been described by Knapp and Török. Most of the successful attempts were made on sclerosed lenses; many cataracts that were thought to be best adapted to this method were found to have friable capsules with rather tough zonulas, and the amount of manipulation necessary to express them in the capsule would have been much greater than would be required to open the capsule and remove

the soft part of the cortex remaining after the expression of the nucleus by stroking the cornea and irrigating the chamber. Even soft white lenses with tough capsules frequently could not be removed by this method because of the difficulty in grasping the capsule; they should, I believe, be removed by some other method. Also juvenile and traumatic cataracts are not easily removed in this manner.

#### DISCUSSION OF CASES

In the past eleven months 24 of 100 extractions were successfully done by combined expression and traction as described above. The extractions were all in elderly persons, mostly over sixty. The time of development of the cataract varied from six months to more than twelve years. In nine of the 24 cases the lenses were large and sclerosed; fifteen were soft, including immature and hypermature lenses and lenses with white fluffy looking cortices. Vitreous was lost in 3 cases, each time due to a squeeze by the patient before the capsule forceps was introduced. In each the vitreous loss was very small in amount. After the lens was grasped the vitreous receded and did not again appear in the wound. One patient squeezed violently as the forceps was applied, expelling the lens still in the grasp of the forceps, and without vitreous loss. Another had a deeply set eye with extremely small palpebral opening (it would not admit my smallest speculum) with atrophic conjunctiva and obliteration of the fornices from old trachoma and pannus. This patient was an old lady who desired better light perception and insisted on having an operation despite an unfavorable prognosis. As the incision could not be made with a knife it was started by a keratome and finished with scissors. The lens was hypermature and delivered easily without loss of vitreous. The patient was discharged in five days with a well healed wound; six months later she could see to get about without glasses.

The twenty-four extractions by combined expression and traction do not include several extractions in which the capsule was ruptured after the lens had engaged in the wound. This happens because of pressure on the cornea as often as from pulling on the forceps, and with either soft or hard cataracts. The collapsed capsule can be removed without difficulty and the chamber irrigated to remove any retained cortex with no more inconvenience than is experienced in doing the ordinary extracapsular extraction. One patient developed iritis with ciliary injection and pain on the third day. The complication yielded,

however, to atropin and moist heat and disappeared by the tenth day. The average length of time which these patients spent under observation after the operation was ten days. Table 1 shows the visual acuity on the first refraction and does not represent ultimate results.

TABLE 1.—FINDINGS IN 24 CASES OF INTRACAPSULAR EXTRACTION OF CATARACTS

Number	Eye	Duration, years	Character of cataract	Operative complications	Complications in after care	Days in hospital		Days after operation	Remarks
							Vision		
1	R	6	H	None	None	11	$\frac{9}{16}$	11	Two hours after operation, patient blew nose violently producing expulsive hemorrhage. Slight reaction third day. Vitreous opacities; lost right eye following operation for cataract six years previously.
2	R	7	H	None	None				
3	L	5	S	None	None	15	$\frac{9}{10}$	14	
4	L	12	H	None	None	13	$\frac{9}{20}$	15	
5	L	2	S	None	None	6	$\frac{9}{6}$	20	Old cyclitis, chorioiditis. Glaucoma right eye. Diabetes
6	L	$\frac{1}{2}$	S	None	Bulging wound, incarceration iris	22	$\frac{9}{18}$	22	
7	R	4	H	Loss of vitreous due to squeeze	None	10	$\frac{9}{12-2}$	11	
8	L	1	H	None	None	8	$\frac{9}{12}$	23	
9	R	1	S	None	None	9	$\frac{9}{60}$	8	Extremely small palpebral aperture. Old trachoma with pannus. Hypermature cataract. Vitreous loss due to squeeze. None during or after extraction. Albuminuric retinitis.
10	L	1	S	None	None	12	$\frac{9}{60}$	17	
11	R	2	S	Patient squeezed out lens	None	15	$\frac{9}{60}$	15	
12	L	9	H	None	None	12	$\frac{9}{0}$	20	
13	R	3	S	None	None	10	$\frac{9}{10}$	10	Chronic facial eczema. Chamber formed and clear at twenty-four hours.
14	R	?	S	Section made with keratome and scissors	None	5	c.f.g.*		
15	L	4	S	Vitreous loss after section	None	20	$\frac{9}{60}$	20	
16	L	1	S	None	None	12	$\frac{9}{60}$	12	
17	R	2	H	None	None	8	$\frac{9}{0}$	8	Amblyopic eye. Lens removed for cosmetic effect. Diabetes, sugar 3.5 per cent two weeks before operation.
18	R	2	H	None	None	11	$\frac{9}{12}$	11	
19	L	6	H	None	Striped keratitis.	9	$\frac{9}{20}$	14	
20	R	10	S	None	Panophthalmia				
21	R	2	S	None	None	11	$\frac{9}{20}$	18	
22	L	2	S	None	None	10	$\frac{9}{60}$	13	
23	L	2	S	None	None	8	c.f.g.		
24	R	1	S	Mild iritis third day		10	$\frac{9}{18}$	15	

\*Counts fingers.

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## THE USE OF RADIUM IN THE TREATMENT OF DISEASES OF THE EYE AND ADNEXA\*

G. B. NEW AND W. L. BENEDICT

The use of radium in the treatment of diseases of the eye and adnexa is becoming more common with the greater availability of the element. Radium has been employed in corneal ulcer, and in inflammatory diseases of the lids and globe, but has been found to be most useful in the treatment of malignant diseases and vascular tumors. Lawson, Ryerson, Williams, and others have reported cases which clearly demonstrate the value of radium in such conditions while Cohen has found it of some use in retarding the development of certain types of cataract.

Vernal catarrh is probably benefited by radium treatment; Pusey and Butler have reported cases in which the treatment was very satisfactory. We have treated 9 cases of vernal catarrh, but are withholding the report of results until we have made a further study of the cases.

It has been recommended that glioma, and melanosa sarcoma shall be treated with radium (Heckel). Its use in glioma, however, is believed to be unwarranted by Horsley and Finzi, who say, "Radium rays from which the less penetrating beta rays have been filtered off exert no influence, discoverable by present methods, in the nerve tissues." The radium has no effect on melanotic tumors comparable with its effect on basal-cell epithelioma or vascular tumors and should be used only after wide removal of the pigmented mass.

Our experience with the use of radium in diseases of the eye has been in two groups of cases, first, those cases which in our judgment should be treated with radium alone, and second, those in which the radium treatment is employed in addition to surgery. The malignant cases are selected on a basis of the character of growth, chronicity, and extent of involvement of the tissues. Various types of epithelioma may be found about the lids and globe as well as within the eye. They may

\* Reprinted from *Am. Jour. Ophth.* 1920, iii, 244-250

be situated on the margins of the lid, at the canthus, or at the limbus. The degree of malignancy will be determined by the type of cell most abundant, and by the location and direction in which the tumor extends. A basal-cell epithelioma may extend over considerable area on the surface of the lids and do less permanent damage than a much smaller, similar epithelioma at the inner canthus which is rapidly extending toward the apex of the orbit.

Epitheliomatous nests that lie deep in the tissues are difficult to reach, and for several months or even years after treatment with radium it is often impossible to determine whether or not the growth has become inactive. A section of tissue which had been subjected to treatment with radium years before for epithelioma was found to be undergoing epithelial cell proliferation and infiltration without evidence on the surface. In some cases, therefore, it is better to remove the involved tissue with the knife or cautery and apply radium later. In other cases radium alone may be sufficient to effect a cure.

The action of radium in infectious diseases of the eye is comparatively slow. Rapidly extending ulcers of the cornea should be treated locally by the remedies commonly employed in addition to the use of radium, if it is used.

#### APPLICATION OF RADIUM

In diseases of the eye and adnexa radium is applied directly in contact with the growth in the form of a plaque, or as emanations.

In treating tumors it is best to insert the emanation or the radium directly into the center of the tumor. In treating superficial lesions the use of the plaque or the radium tube directly against the skin is the preferable method. We have not used any screening in these cases, except the rubber finger cot that encloses the radium tube or plaque. It is desirable that the cornea shall be protected in treating lesions of the lid in order to prevent severe reaction, but we have not seen any serious effects on the cornea from the use of radium. For this we have used a screen of lead 2 mm. thick.

In treating lesions of the cornea, the eye is cocainized, a self-retaining retractor inserted, the radium placed in a lead applicator, and an area of the radium is exposed the size of the lesion to be treated. A nurse holds the applicator in position directly in contact with the lesion for as long as it can be borne comfortably by the patient,



usually from fifteen minutes to one-half hour. It is essential in treating lesions around the eye that all radium applications shall be given within ten days so that the treatment will be completed before the radium reaction begins from ten days to two weeks afterward, lasting for from two weeks to one month. The patient is advised to leave the area during this time open to the air as much as possible and to cleanse it with boracic solutions.

#### TYPES OF CASES TREATED

Cases.....	133
Angioma of the lids.....	10
Blastomycosis of the lids.....	3
Vernal catarrh.....	9
Basal-cell epithelioma of lids and canthus.....	97
Epithelioma of the limbus.....	2
Sarcoma of the orbit.....	12

#### ANGIOMA OF THE LIDS

Radium is specific for angioma, lymphangioma, and hemangioma. The best results are obtained in young children, and in this group the angioma may be removed with but little if any deformity.<sup>6</sup> In treating the cavernous type, the radium is used in the form of a very small tube which is inserted into the center of the tumor through a small incision in the normal skin close to it. A small pointed forcep is used to burrow into the tumor in the same manner that a blister is opened. The radium tube, attached to a silk thread, is inserted through this channel and left in place several hours, depending on the number of milligrams used and the size of the tumor. The results in this group of cases have been especially satisfactory; most of the tumors disappear in three or four months with one treatment. Superficial angiomas are treated by means of a 5 mg. plaque kept moving over the entire area, thus distributing the treatment evenly.

#### BLASTOMYCOSIS

Blastomycosis is treated by holding the radium tube or plaque directly over the lesion. The tissues about the lesion should be screened with lead 2 mm. thick in order to protect them from the rays. The patient should be seen about every six weeks so that if the first treatment is not sufficient to clear up the lesion it may be treated before the condition has a chance to become more extensive.

## BASAL-CELL EPITHELIOMA

Basal-cell epithelioma of the lids without involvement of the tarsus or bone may be entirely removed by radium treatment. The type of epithelioma and its location should be carefully considered before radium is recommended for lesions around the eyes. If the lesion appears to be active and extending rapidly, in all probability it is squamous-cell epithelioma which has developed on basal-cell epithelioma and does not respond to radium so well as the basal-cell type, and therefore should be removed by excision with the knife, or knife and cautery, and the open wound treated with radium. If bone is involved and there is a reasonable chance of eradicating the trouble, the growth, and the eye if necessary, should be removed, the bone thoroughly cauterized with soldering irons, and radium used in the open wound. Temporizing in the treatment of epithelioma, especially epithelioma around the inner canthus, is frequently the cause of failure to cure. Radium eradicates the growth in a very large percentage of cases of basal-cell epithelioma involving the lids but not the tarsus or bone. The patient should return for observation about every six weeks for several months, so that if the trouble is not entirely eradicated by the first treatment, further treatment may be given. However, a large dose of the radium should be given at the first treatment since frequently the lesion treated with small doses is only aggravated, and the possibility of clearing up the trouble is diminished.

Melanotic tumors should not be treated with radium, but a radical operation to remove the growths should be done, since this is the only means of eradicating the malignancy. A general anesthesia should be employed and the excision made very wide of the growth. If a local anesthesia is used there is always a possibility of traumatizing some of the cells of the tumor. A plastic operation should not be done on the lids for at least six months after the removal of the growth because it tends to cover up the area in which the recurrence may take place.

## SARCOMA OF THE ORBIT

Sarcoma of the orbit is best treated by inserting the radium in the form of a tube directly into the tumor. It is well also to ray the parotid and submaxillary glands as a prophylactic measure. In our cases of young children the sarcoma has been reduced in size or entirely



FIG. 290.—(Case 214143). Sarcoma of orbit, Feb. 25, 1918, before treatment with radium.



FIG. 291.—Patient shown in Figure 290, April 17, 1918, after treatment.

eradicated, but on account of the marked malignancy, the patients generally die because of metastasis; by the removal of the primary tumor, however, we believe the child's life is increased by months and sometimes by years. In adults, the prognosis is much better; we have been very much encouraged by the use of radium in these cases, but we are not able to state what the ultimate results will be.

#### SARCOMA OF THE ORBIT

Case 214143. A man, aged 61, who was examined Nov. 16, 1917, had noticed diminution of vision in the right eye for eight years. He consulted an oculist who told him that he had a detached retina. Two years later the vision in the eye was completely gone and the intra-ocular tension was high. In another two years, because of frequent attacks of pain, the eyeball was removed. Fat was taken from the abdomen and transplanted into the orbit. Over this a shell eye was fitted and worn without difficulty until one month before the examination in the clinic.

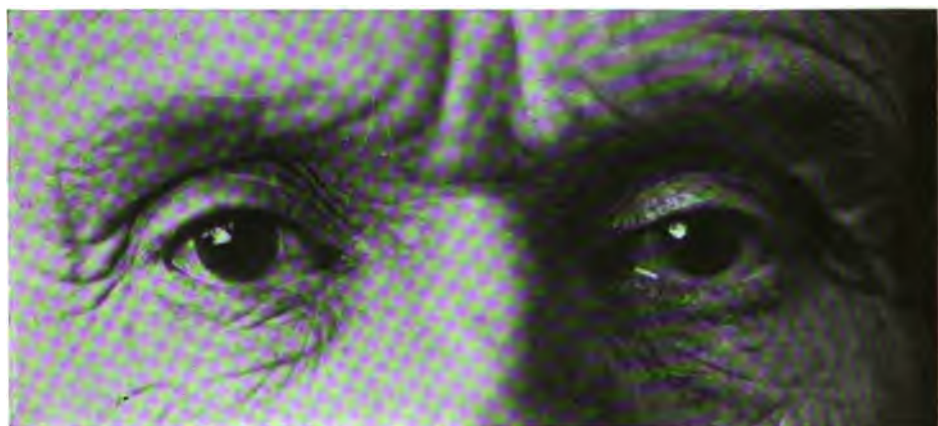
On examination a mass was found in the anterior part of the right orbit under the lids. The palpebral fissure was open about one-quarter of an inch. The mass was covered by thickened hypertrophic conjunctiva with some edema in its lower and outer part, and a bluish discoloration over the inner third. Over the central part of the mass was another bluish discoloration, 7 or 8 mm. in diameter, slightly elevated, which did not disappear under pressure. There was no tenderness nor soreness around the mass on palpation; it was freely movable in all directions except from the lower inner quadrant; even there it did not appear to be attached to the periosteum. The patient was able to wear a shell eye over the mass without the appearance of proptosis, but the laxity of the lower lid gave the appearance of an ill fitting eye. The pre-auricular or submaxillary glands were not swollen or tender. The condition was diagnosed sarcoma of the orbit. Feb. 28, 1918, 50 mg. of radium were inserted directly into the tumor and left in place twenty-four hours. The patient returned for observation April 23. The greater part of the tumor had disappeared although there was a slight thickening in the inner and lower part of the orbit. At that time 100 mg. of radium were inserted into this part of the orbit for twelve hours. The patient returned again June 26 with the condition entirely cleared up (Figs. 290 and 291).

## EPITHELIOMA OF THE CORNEA

**Case 230977.** A man, aged 59, was examined May 10, 1918. One year before the patient had noticed a growth which started as a small, red elevated area near the limbus of the left eye. Growth was rapid



**FIG. 292.**—(Case 230977). Epithelioma of the cornea, May 11, 1918, before treatment with radium.



**FIG. 293.**—Epithelioma of the cornea Figure 292, July 7, 1918, after treatment.

and continued until the nasal half of the cornea was covered by a granular, elevated, sloughing mass. Epithelioma of the cornea was diagnosed.

A 50 mg. tube of radium was used daily in half hour treatments over the area on the cornea for a period of ten days. The eye was

cocainized, a self-retaining retractor was inserted, exposing an area the size of the lesion to be treated, and the radium held in place with a lead applicator.

July 29, 1918 all macroscopic evidence of epithelioma had disappeared from the cornea. There was some roughness of the ocular conjunctiva near the limbus, on the nasal side, which extended over on the cornea for about 1 cm. in the region previously occupied by the tumor mass. The cornea was slightly vascular and infiltrated. There was no elevation and no fibrous scar tissue. The visual acuity of  $\frac{6}{60}$  which the patient possessed at the time of the first examination was not decreased (Figs. 292 and 293).

#### EPITHELIOMA OF THE RIGHT UPPER AND LOWER LIDS

Case 200985. A man, aged 67, who was examined July 10, 1917, stated that ten years before a slight growth had appeared at the right inner canthus. Two years later, the growth having extended, a plaster was applied over it and part of the tissue removed. The lids apparently healed, but about six years later the growth recurred. On examination the lids showed a horseshoe shaped epithelioma involving the inner half of both upper and lower lids and the inner canthus of the right eye. This mass was elevated, indurated, and pink. It was covered by small scabs and a greyish discharge. The palpebral and ocular conjunctiva also showed moderate congestion.

The patient was given twenty-six hours of treatment with a 50 mg. tube of radium; the treatments extended from July 12 to July 27.

Two months later radium was again applied for twenty hours, a 50 mg. tube being used daily from August 31 to September 12.

The eye and surrounding tissue were protected during these applications by a 2 mm. lead screen. No screening of the radium was used, except the container, which is a silver tube (Figs. 294 and 295).

#### BLASTOMYCOSIS OF THE RIGHT LOWER LID

Case 205095. A boy, aged 17 was examined Aug. 15, 1917 for a growth on the inner two-thirds of the right lower eyelid. This growth was about one and one-half inches long and one-half inch wide; it involved the lid margin, the conjunctiva, and the skin below the lid. The surface was scaly and brown. A diagnosis of blastomycosis

was made. A 50 mg. tube of radium was applied over the diseased area on the lid daily for six days; the total time of exposure amounted to ten hours. The eye and the tissues surrounding the lesion were protected by 2 mm. of lead. The patient was given a prescription for



FIG. 295.—Patient shown in Figure 294, Oct. 26, 1917, after treatment.



FIG. 294.—(Case 200985). Epithelioma of right upper and lower lid, July 11, 1917, before treatment with radium.

potassium iodid and advised to return in six weeks, at which time the growth on the lower lid was entirely cleared. A new area of the disease, however, had appeared on the right upper lid, which received ten hours exposure of a 25mg. plaque of radium during the next four

days. December 12 the patient returned with no recurrence, but at this time the reaction from the last application of radium had not entirely subsided. A recent letter states that his trouble has not recurred.



FIG. 297.—Patient shown in Figure. 296, March 27, 1917, after treatment.



FIG. 296.—(Case 182293). Epithelioma perforating the left upper lid, Jan. 6, 1917, before treatment with radium.

#### EPITHELIOMA PERFORATING THE LEFT UPPER LID

**Case 182293.** A man, aged 76, with an epithelioma on the left upper eyelid was examined Jan. 6, 1917. The growth has appeared nine



years before and a physician had cauterized it at intervals for the past one and one-half years. This epithelioma involved the entire upper lid and extended into the upper part of the orbit, perforating the lid.

Twelve hours of applications of a 50 mg. tube of radium and one hour of a 25 mg. of radium plaque were given the patient over a period of ten days.

The last photograph taken March 27, 1917 shows the condition to be entirely healed (Figs. 296 and 297).

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## TREATMENT OF CHRONIC DACRYOCYSTITIS\*

W. L. BENEDICT AND R. A. BARLOW

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Inflammation of the lacrimal sac may be said to have become chronic when the function of the drainage apparatus cannot be restored by the use of medical and hygienic measures, and operative procedures have to be employed either to restore function of the duct or to remove the sac and obliterate the duct. Malformation of the puncti, eversion of the lids, simple stenosis of the duct, or obstruction of the lacrimal meatus in the nose may be responsible for epiphora at any age without inflammation of the sac, while acute or chronic inflammation may arise without complete closure of either end of the drainage system. Stenosis of the duct in infants seldom results in suppurative affection of the sac but may often cause collections of large amounts of secretion that distend the sac, producing a mucocele and often a permanent fistula through the skin. Such a mucocele may extend backward, involving a part of the ethmoid labyrinth, or even extend into the orbit. Obstruction in children may follow edema and secondary inflammation of the duct from syphilitic periostitis without other obstruction. The lacrimal sac in such cases may become secondarily infected and produce a purulent secretion. The sac is quite troublesome and difficult to heal except by vigorous antiluetic treatment. If we may draw a conclusion from the comparative occurrence of purulent discharge in cases of obstruction of the lacrimal system we may say that chronic suppurative dacryocystitis in children is more often the result of disease of the structures about the lacrimal duct and sac than of congenital or acquired anatomic obstruction to the patency of the system.

The proportion of suppurative conditions of the sac in the adult is reversed. Obstruction to the flow of tears follows atresia of the puncti, eversion of the lids, or intranasal blocking. With the latter cause the closure of the canal is usually found in the duct at the point of least diameter, 10 mm. to 15 mm. below the upper end of the duct

\* Reprinted from *Am. Jour. Ophth.*, 1919, ii, 843-849.

proper. Rarely we may find the entire duct occluded and contracted to a small fibrous cord. The secretion collecting in the sac regurgitates into the conjunctival culdesac, or it may be thus emptied by external pressure. Occasionally the obstruction may be in the canaliculi and the collected secretion expressed through a stenosed duct or artificial opening into the nose. Both the upper and the lower openings may be closed, leaving a blind pouch which becomes an immense mucocele or which may rupture externally, producing a permanent fistula.

The treatment of chronic dacryocystitis is ultimately surgical. The procedure to be employed will depend on the nature and position of the obstruction, the extent of the involvement of contiguous structures, and the changes in the tissues produced by the disease or by previous treatment. The inflammation may be of low grade producing a mucopurulent discharge without redness, pain, or heat, showing only a moderate and varying swelling and loss of function. Atony of the muscles of the lid and the muscle of Horner may fail to empty the sac completely and a passive dilatation of the sac results. The contents may be expressed easily.

Collection of secretion purulent or non-purulent will, if rapidly produced, set up signs of active inflammation which give rise to acute exacerbations. Removal of obstruction to the intranasal portion of the duct and careful use of small probes will be sufficient in many instances to reestablish patency of the duct. Further attention, such as irrigations and local application of antiseptic and astringent lotions, may be employed until the lining of the duct is in a more nearly normal condition. If the inflammation has existed for a long time, if there have been frequent attacks of acute inflammation, or if a quite dacryocystitis has been unsuccessfully treated by the use of large probes, such simple measures as would be given to the lower end of the sac with the use of small probes will not insure a permanent opening, and it will be necessary to employ more radical measures.

Primary disease of the sac, that is from foreign material having become lodged in the sac or duct, producing stenosis and permitting secondary infection, may become so extensive as to occlude the entire duct and set up a periostitis and disease of the contiguous accessory sinuses. This is seen frequently in cases of traumatism of the nose and orbit from a kick in the face by a horse, or other accident, in which the head has suffered a crushing injury. On attempting to

sound such a duct the sounding instrument will encounter bare bone, loose pieces may be felt to move, and the instrument may be passed beyond the lacrimal fossa into the opened cells of the accessory sinuses, and even into the nasal cavity beneath the nasal mucosa. If the nasal mucosa is also broken the secretion may empty directly into the nose. That this does not always follow is sufficient evidence that operative procedures intended to produce such and only such an opening are inadequate, whether the opening is made with a probe, a trephine, or a chisel.

Secondary disease of the sac may follow disease of the accessory sinuses. We have been slow to recognize the importance of this fact because of the difficulty of diagnosing disease of the anterior ethmoid cells. Little evidence of ethmoid disease may be found by inspection of the nasal chambers at the time of examination. The nose may appear negative, yet in such cases we frequently have demonstrated mucopurulent secretion with destruction of the lining of the cells, when we have made an external opening for extirpation of the sac. Inflammations of this nature are, of course, quiescent; they may exist for years without giving sufficient evidence of disorder to warrant extirpation. Drainage is established through or around the sac, and the mucopurulent secretion is expressed into the conjunctival culdesac. Most of the secretion comes from the changed mucosa of the sac itself, and removal of the sac may close the drainage and so cover the evidence of ethmoid disease. Occasionally, however, a permanent fistula may be established through the skin, through which the mucopurulent secretion of the diseased ethmoid cells escapes.

A suppurative ethmoid may, by its very close relation to the lacrimal groove, set up an inflammatory process in the duct or sac which sooner or later may become purulent. The ethmoiditis may be of very low grade, and give no intranasal manifestation of its presence, but in time the presence of the pus may cause inflammatory reaction in the lacrimal duct which in turn may lead to stenosis, predisposing to a suppurative condition in the sac.

Pus may find its way into the lacrimal duct through the meatus where there is a suppurative sinusitis with free drainage into the nose. Under such conditions the patient in blowing his nose forces the pus into the duct. Simple extirpation of the sac does not cure the symptoms of chronic dacryocystitis in such cases. We admit the truth of the statement so frequently made, that if all the sac is removed the

discharge will stop, but we are referring to the cases in which healing does not take place when the sac is totally destroyed or removed.

To dispose of the troublesome and dangerous secretion in chronic dacryocystitis is the high aim of treatment. If at the same time function of the duct can be restored a double aim will have been accomplished. To this end various operations have been devised, but insufficient consideration has been given the changes which must be made in the tissues involved, for after all either the offending part is removed completely, or the elements are so rearranged that nature will not be impeded in providing protection for healthy organs and other tissues. To remove or to destroy a sac is to admit inability to cope with the disease of the tissues involved. The function of a stenosed and diseased lacrymal sac may often be restored by an operation no more difficult to perform than that of extirpation of the sac.

As has been mentioned, function may be restored in some cases by removal of low nasal obstruction and the careful use of small probes. The use of large probes, however, should be avoided in all cases. If a canal or bony foramen needs to be enlarged it should be done by an open method, using cutting bone instruments, and not blindly by forcefully probing, crushing, and tearing tissues that cannot be seen, and are only indefinitely felt. To attempt the treatment of chronic dacryocystitis by use of large probes either to enlarge the duct or to make an artificial opening into the nasal chamber is unwarranted and unjustified by the results obtained. If false passages are made into the antrum or soft tissues of the cheek troublesome complications may follow. The use of metal styles is happily on the decline but they are now encountered sufficiently often to warrant mentioning the dangers accompanying their use and to urge better surgical methods of securing the same result.

Destruction of the sac by actual or potential cautery accomplishes only one thing—it stops the secretion from the tissues destroyed. It does not allow inspection of the tissues surrounding the sac either from within or without. It does not aid in reconstruction. No attempt is made to restore function to the sac. It is as difficult to destroy the sac by cautery with good cosmetic effect as it is to extirpate the sac, and the latter procedure has the added advantage of allowing inspection of the fossa and the bony duct, leaving nothing to be desired from the cosmetic standpoint.

Extirpation of the sac after the method of Meller gives most satisfactory results in most cases. After the sac has been removed a sound should be passed along the entire bony surface of the fossa and upper part of the duct in a search for openings into accessory cells and pieces of loose or necrotic bone. If any opening is found it should be enlarged and the cavity from which it leads explored and cleaned. If only one or two cells can be found to be involved, and the disease is not then giving rise to a purulent discharge, the whole cavity may be irrigated with 1 : 2000 bichlorid of mercury solution, and the wound closed in the usual manner without drainage. If the bone is necrotic or if pus is present in the ethmoid cells the loose bone should be removed, the diseased cells broken down, and an opening made through the nasal mucosa. The external wound may then be closed and the ethmoid disease treated from within the nose.

Operations for the restoration of function of the sac and duct as well as the cleaning out of any diseased ethmoid cells have been advocated from time to time and have more to be said in their favor than any other form of treatment of chronic dacryocystitis. We are convinced that it is not necessary in the majority of cases to do a radical operation from the external surface. Plastic operations intended to restore function are unnecessary, beside being difficult to perform and involving a great deal of after-treatment. When the sac and upper portion of the duct have not been destroyed the duct may be tapped from the nasal side by a procedure that at the same time will allow exposure of the anterior ethmoid cells and take care of any other intranasal obstruction.

If a sound can be passed through the sac and into the upper part of the duct the sac should not be extirpated, but an attempt should be made to restore the function of the duct by means of intranasal dacryocystostomy. The operation should be done by one who is familiar with intranasal technic. If for any reason the operation should not accomplish the result desired the sac may always be removed later. West, Yankauer, Paterson and Fraser, and others report excellent results. They have restored function to the lacrimal drainage system in a large percentage of cases in which operation was done, which is vastly more than can be said for the extirpation or cautery method of treatment.

An operation which restores function of the sac and provides adequate drainage of diseased ethmoid cells in the neighborhood of

the duct, should any be present, should be easy to perform and unattended by complications that will require long after-treatment. Such an operation may be described as follows:

#### OPERATION

Two or three drops of 1 per cent cocain solution are instilled into the eye. This allows the probe to be introduced into the punctum with little or no discomfort.

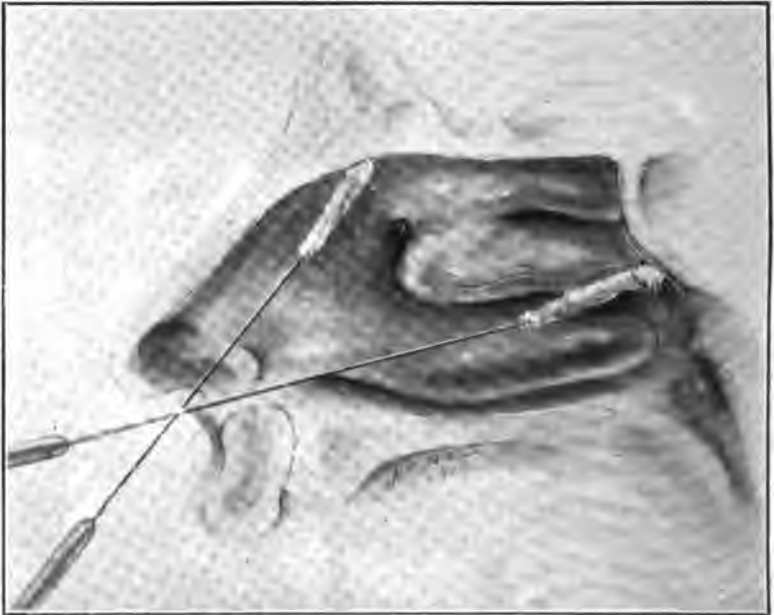


FIG. 298.—Showing method of applying cocain mud with adrenalin to sphenopalatine ganglion and anterior ethmoidal nerve, giving complete anesthesia.

The intranasal anesthesia is obtained by blocking the sphenopalatine ganglion and the anterior ethmoidal nerve by introducing a cotton applicator impregnated with cocain mud, with adrenalin as the solvent, beneath the posterior end of the middle turbinate, and a second applicator passed between the septum and the middle turbinate to the cribriform plate as may be seen in Figure 298. These applicators are allowed to remain in position ten minutes, which ordinarily gives complete anesthesia of the nasal chamber. In case of high or anterior septal deflection a submucous resection of the septum should be done at this time.

A lacrimal probe is now introduced through the lower punctum (without slitting the canaliculus) into the sac and duct as far as it will go, and allowed to remain. This serves as a guide and landmark. The surgeon while working in the nose is thus constantly reminded of the direction of the duct.

The mucous membrane of the agger nasi is now elevated and resected and a flap about 1 cm. in diameter is removed just in front of the attachment of the middle turbinate. The bone is next removed



FIG. 299.—Mucous membrane flap removed, exposing bone ready to be chiseled, *a*. Bone removed, exposing nasal wall of lacrimal duct and sac.

by means of a small chisel to make a window slightly smaller in diameter than that of the mucosal opening (Fig. 299). This exposes the inner wall of the lacrimal sac and the upper part of the duct (Fig. 299*a*). Any diseased ethmoid cells which are discharging their contents into the duct can be easily exenterated at this time.

The lacrimal probe is now withdrawn slightly until the tip causes a tenting of the sac wall into the opening made through the bone (Fig. 300). With a small knife the sac is incised (Fig. 301), the flap



is grasped with a fine forceps, and the incision continued in a circular path, completely removing this portion of the sac wall (Fig. 301*b*). The probe is now removed, and the sac irrigated through the punctum.



FIG. 300.—Probe inserted through inferior punctum, extending it into the sac and tenting it through window opening into the nose.

This completes the operation and gives adequate drainage into the nose. Very often a quantity of pus escapes into the nose when the

first incision is made into the sac wall. The after-treatment is almost nil. No packing is necessary. The patient should be cautioned not to blow the nose vigorously, as the secretion from the nasal chamber may be blown through this new opening into the conjunctival sac.

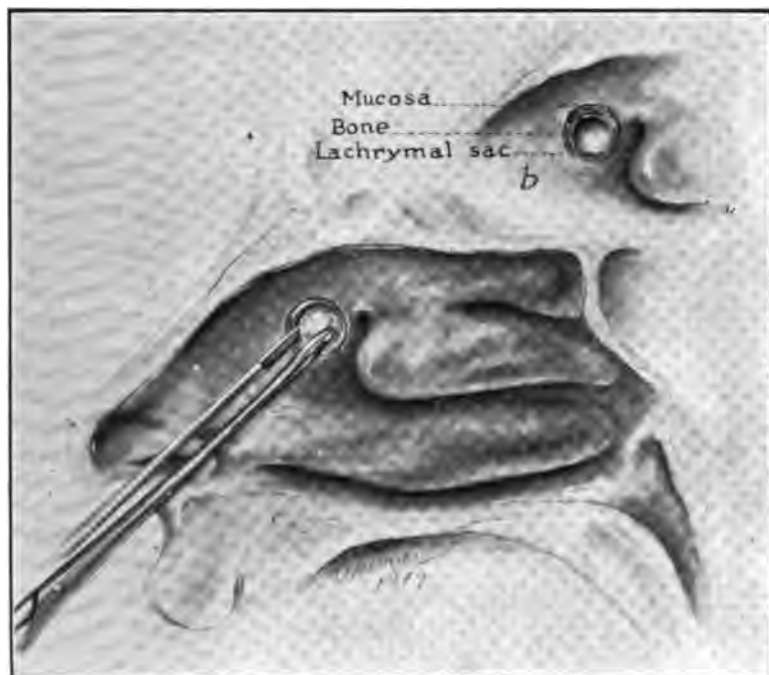


FIG. 301.—Sac wall tented through window opening, grasped by forceps, and beginning incision. *b*, Window opening into sac completed, draining freely into nose.

The reaction is very slight, healing is rapid, with little contraction of the mucous membrane. The patients experience no epiphora nor other discomfort after the operation. A lotion of zinc sulfate and adrenalin solution is used for the first week following operation, after which time no further treatment is needed.

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## MASTOIDITIS, ACUTE AND SUBACUTE. RESULTS IN A SERIES OF OPERATED CASES\*

H. I. LILLIE AND R. A. BARLOW

In cases of acute and subacute mastoiditis operation is generally indicated in order to remove the suppurative process of the bone and to preserve the hearing function. In the presence of a complication such as extension of the suppurative process to the meninges or to the blood stream through the lateral sinus, the operator is confronted, not with the advisability of entering the mastoid process, but with the responsibility of saving life. Fairly early and complete operation will in a large measure avoid such responsibility. The less immediate serious possibility is the chronically discharging ear now generally considered by the life insurance companies as grounds for rejection of an applicant.

The literature of the last ten years furnishes few reports of series of cases in which operation was instituted in acute or subacute mastoiditis. Two of the more important articles are by Welty and by Borries. From the records in Mygind's clinic in Copenhagen Borries collected 1108 cases in which the total mortality was 10.7 per cent. The operation was considered the cause of 14 of the 119 deaths. Thus the mortality due to operation *per se* is reduced to 1.4 per cent. Welty reports 106 cases operated on with no loss of life. In his series there were six sinus thromboses, one temperosphenoidal abscess, and three serous meningitis cases. Welty advocates the complete exenteration of the mastoid process. He has not had to reoperate in any of these cases.

The evolution of the operation for mastoid abscess is interesting. Surgical interference has passed through the stage of simply incising the subperiosteal abscess resulting from rupture through the bone, uncovering the bone and breaking off the outer table to allow better

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drainage, to the now recognizedly advisable procedure of exenterating completely the mastoid process. Far better results are obtained by the latter method.

The 64 patients in our series of non-selected cases were operated on between July 1, 1917 and Jan. 1, 1919.

The age incidence in this series is noteworthy because relatively the same number of cases represented each of the first five decades. The youngest patient was three and one-half months, the oldest, seventy-two years. Mastoiditis is evidently not confined to any one period of life.

The trouble in the ear had persisted on an average of four weeks before the patients came for consultation. In 44 of the 64 cases the abscess in the ear had ruptured spontaneously before the ear had even been examined. In no region of the body has pain with temperature and other symptoms of infection been considered more lightly by the laity and by a great many physicians than pain in the ear. The person with abdominal pain and a high temperature lasting but a few hours is very liable to lose his appendix. There seems to be no reason why the suffering of the patient with an abscessed ear should not be relieved early by incision of the drum membrane rather than late by spontaneous rupture. The longer the ear remains undrained the more certain is the development of the surgical mastoiditis. Every physician can and should know when looking into an ear whether the ear should be drained. Bacteriologic examination of the first pus is very important because it often gives warning as to the character of the suppurative process and prepares one to institute operation for thorough drainage of the mastoid at the earliest sign of extension. Disease of the mastoid is not in itself a possibility of great danger, but extension to the meninges or involvement of the blood stream through the lateral sinus are complications which offer grave prognosis, and frequently might be avoided.

The indications for operation in the series of 64 cases were significant:

1. In 40 cases the swelling behind the ear pushed the ear outward, tenderness was exquisite; in other words, the cases bore a diagnostic label.
2. In 14 cases the diagnoses were not definite from a general standpoint but were definite from the ear standpoint. These patients had a history of discharge of several week's duration without a tendency

to subside, pain at night causing more or less insomnia, and general lassitude; in these patients we have found either the lateral sinus or the dura uncovered by the disease process.

3. Ten cases in which the diagnosis was indefinite from the general standpoint presented definite evidence of extension of the suppurative process from the ear standpoint.

Two of 6 patients with sinus thrombosis required jugular ligation and section; 2 had suppurative meningitis, one perisinus abscess with septic nephritis, and one Bezold's abscess of the neck.

What we choose to call the complete mastoid operation, rather than simple mastoidectomy, was used in all the cases but one, and in none in which the condition was in the acute or subacute stage has it been necessary to reoperate. In the one case, that of a young man, a musician with a six months' history, the otorrhea did not subside completely. Because the patient had retained very good hearing function which we wished to preserve the conservative operation was done. This was perhaps faulty judgment on our part. In no case were the findings less serious than we expected and in most cases they were more serious than we had expected.

The postoperative stay in the hospital of the patients of this series averaged six days. Forty-eight patients had no postoperative incident while in the hospital; those in whom the sinus or meninges were involved had a stormy convalescence. One patient with pleurisy with effusion and a respiration rate of 70 per minute, on whom we operated for sinus thrombosis under local anesthesia, was very ill for three weeks. A boy with a severe septic nephritis and sinus thrombosis was very sick, and under the care of the pediatricist for several weeks. The patients with meningitis died. It is questionable whether they should have been operated on in the face of such odds.

The average time for complete healing was thirty-one plus days. By complete healing we mean that the ear is dry and the posterior wound closed. Surprisingly little posterior deformity resulted in most instances. The open method of dressing was greatly modified so that only the lowermost portion of the wound was allowed to remain open; the upper portion healed by first intention. Four patients were discharged in fifteen days; one, an old lady, for whom dichloramine-T was used with little tendency to repair, was discharged after one hundred twenty-eight days.

Two old men developed erysipelas while registered as out-patients, one three weeks after operation, the other six weeks after operation; both died. One boy developed smallpox during an epidemic but recovered.

Four patients died, 2 had meningitis prior to operation, and 2 had postoperative erysipelas.

In 3 cases the otorrhea persisted; the disease, however, was really in the chronic state at the time of operation after which the discharge was greatly decreased.

One posterior wound in a boy with a tuberculous process has not healed completely. He has since had a radical operation but the discharge from the ear continues.

The hearing was improved or remained the same as previous to operation in all but 5 cases. In fact, the hearing function is as good postoperatively as previous to the ear involvement.

#### CONCLUSIONS

1. Early incision of the drum membrane is imperative in inflammatory conditions of the middle ear.
2. In cases of definite mastoiditis operation is indicated reasonably early. The mortality is practically nil in the uncomplicated cases.
3. Preservation of the hearing function is fairly certain.
4. Secondary operation is rarely indicated if the mastoid process is exenterated completely.

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## RHINOPHYMA\*

G. B. NEW

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The condition known as rhinophyma is somewhat unusual; it is an occasional sequel of acne rosacea. The nose becomes swollen and bulbous, and is covered with soft lobulated, nodular areas that are separated by deep fissures. In some instances the organ is so large as to obstruct vision. Keen reported a case of a patient who could not take fluid with a spoon without first holding his nose out of the way. Wende and Bentz also report a case of large rhinophyma.

Decortication of the nose is the accepted treatment for this condition, but from the fact that such procedure is delayed, and that extended medical treatment is employed, it would seem that the excellent results obtained by operation are not generally known. Warren and White, Keen, Fowler, Wood, Heinick and Sequeira have reported cases in this country in the last fifteen years in which the excellent cosmetic results following decortication are shown. The history of the case observed in the Mayo Clinic is as follows:

Case 254933. C. A. H., a man aged 60 (hotel proprietor), a moderate user of alcohol, coffee, and tobacco, came for examination Jan. 3, 1919. The patient gave a previous history of lues, gonorrhea, and grippe. He complained chiefly of the condition of his nose, which was very large, of pain in the right side of the abdomen, and of gastric distress. The large tumor of the nose was very troublesome, particularly in reading, as well as being a source of embarrassment. An irritation of the nose, face, and chest, which was gradually becoming worse, had existed for twenty years. The enlargement of the nose had been more marked the last two or three years, and had been treated extensively without improvement. The pain in the right abdomen dated back four or five years, but the indefinite gastric distress had lasted for fifteen years.

Figure 302 shows the large rhinophyma. The acne rosacea extended over the cheeks, chest, and back. The Wassermann was

\* Reprinted from *Laryngoscope*, 1919, xxix, 391-395.



FIG. 302.—(254933). Rhinophyma before operation.



FIG. 303.—(254933). Patient shown in Figure 302, two weeks after operation.



negative. The abdominal distress was attributed to duodenal ulcer. Jan. 10, 1919, under ether anesthesia, a large mass of the hypertrophied tissue was cut away with a knife from the dorsum of the nose. The skin covering the lateral portion of the nose was undermined and a mass of tissue was removed from either side. The slight amount of bleeding was readily controlled by hot saline compresses. The margins of the wound were sutured in the midline. Feb. 3, 1919, the surplus tissue was shaved off with a knife down to the framework of the nose. By passing the index finger of the left hand alternately into either nostril the thickness of the hypertrophied tissue could be felt and the rhinophyma was trimmed down in much the same manner that a piece of wood is whittled. Hot salt compresses readily controlled the bleeding and after the first two or three days the wound was left open as much as possible. A dressing of paraffin mesh was placed so as to form a bridge over the nose; it was attached to either cheek with adhesive plaster. No skin graft was employed. Two weeks after the operation the entire nose was completely covered with epithelium (Fig. 303). Small islands of epithelium, spreading out from the epithelium of the glands over the nose, gradually covered the raw area.

Rhinophyma occurs nearly always in males and in most of the cases reported the patient was more than fifty years of age. The condition is classified as belonging in the third stage of *acne rosacea*, which frequently involves the cheeks. Alcoholism, dietetic disorders, and exposure to inclement weather are supposed to be etiologic factors of the condition, but this is difficult to prove. The histories of the cases reported in the literature do not bring out any definite etiologic factor.

Microscopically the connective tissue shows hyperplasia, hypertrophy and increase in the number of sebaceous glands, and enlargement and lengthening of the ducts. The blood vessels are dilated and increased in number. There is marked round cell infiltration in the connective tissue (Fig. 304).

Wende and Bentz have given a very complete pathologic analysis of rhinophyma. Coplin, who examined Keen's case pathologically, called it a soft fibroma with distention of the acne and possibly a hyperplasia of the sebaceous glands.

The treatment consists in paring off the hypertrophied tissue, care being used not to penetrate into the nasal cavity. The paring may be done with a knife or a pair of scissors. The operative treatment of rhinophyma is very simple, and should be followed in these cases.

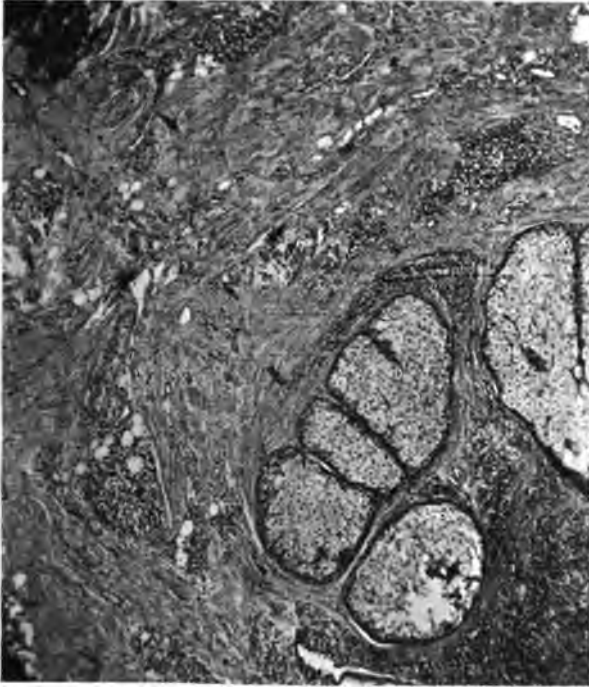


FIG. 304.—(254933). Photomicrograph of rhinophyma. Note the marked fibrosis, the hyperplasia of sebaceous glands, and round-cell infiltration.

Radium has been used, but the results have not been so satisfactory as those obtained by operation. Wood believes that skin grafting is essential for the best cosmetic results. White, Keen, and Heinick allowed the wounds to epithelialize without grafting. It would seem that if the hypertrophied tissue is removed, leaving a smooth surface, that islands of epithelium will appear from the epithelium of the glands of the nose and quickly cover over the raw area, giving a good cosmetic result.

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# SQUAMOUS-CELL EPITHELIOMA OF THE LIP: A STUDY OF FIVE HUNDRED THIRTY-SEVEN CASES \*

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Of all the malignant neoplasms with which man is afflicted, few cause more concern and inconvenience than that of epithelioma of the lip. In the past pathologists have been content to classify cancer of the lip as cancer, without any distinction as to the degree of malignancy. It is a well established fact that some cancers of the lip are fatal to patients and others are not. There must be a reason for this. One theory is that some persons are resistant to cancer, and this seems to be borne out in a certain percentage of cases.

Undoubtedly a large proportion of cancer cells are destroyed by the defense cells of the body; of these the fibrous connective tissue cell is the most important, since it cuts off nourishment from the cancer cells.

The endothelial leukocyte and lymphocyte evidently also play an important rôle in the destruction of cancer cells for practically always they may be seen in the neighborhood of a cancerous growth. Foreign body giant cells that are most probably formed from the endothelial leukocytes are not infrequently found lying adjacent to cancer cells.

The most important factor in squamous-cell epithelioma of the lip seems to be the degree of cellular activity. The cells of some epitheliomas of the lip show a marked tendency to differentiate, that is, to produce a growth similar to the normal; the pearly body is an example. The pearly body corresponds to the horny layer of the epidermis. In other squamous-cell epitheliomas there is no differentiation whatever. In the large majority of growths whose cells do not show a tendency to differentiate, or at least very little, there are many mitotic figures.

In studying these epitheliomas, therefore, it occurred to me that they should be graded according to differentiation and mitosis, special stress being laid on the former. The grading was made on a basis of 1 to

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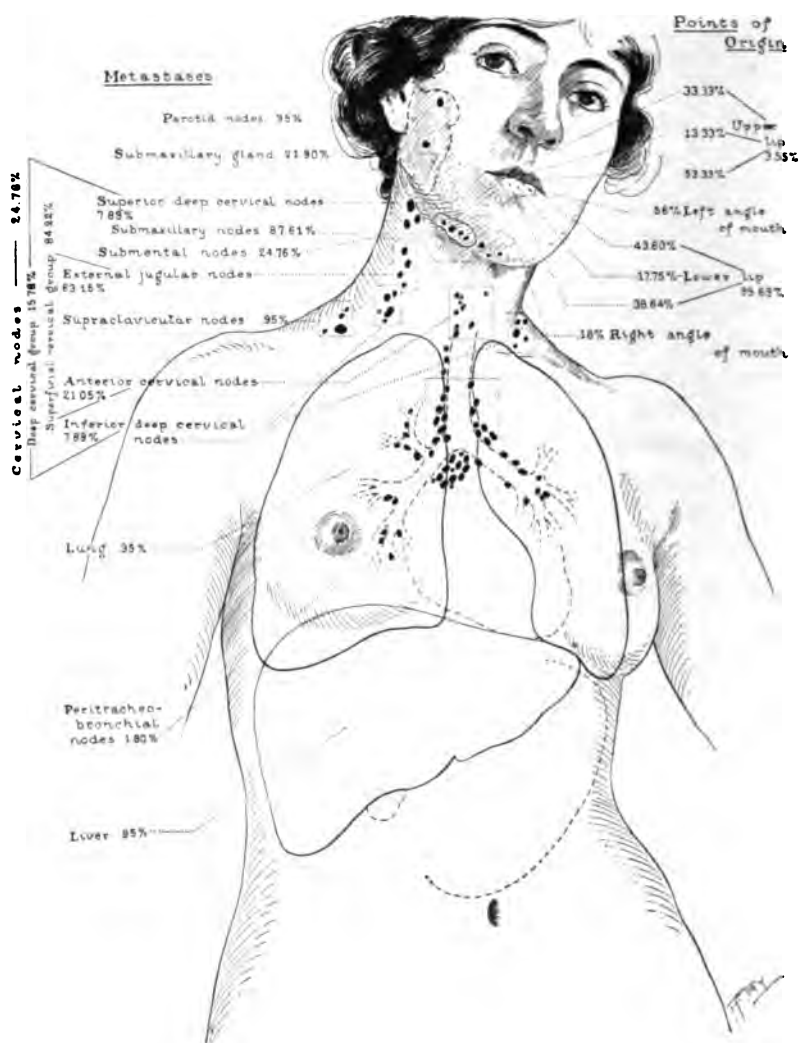


FIG. 305.—Percentages of points of origin of epithelioma of the lip, and percentages of location of metastasis.



FIG. 306.—(a188878). Typical elevated or wart-like epithelioma of the lip.



FIG. 307.—(a265421). Typical depressed or ulcer-like epithelioma of the lip.

4 and absolutely independent of the clinical history. If an epithelioma shows a marked tendency to differentiate, that is, if about three-fourths of its structure is differentiated epithelium and one-fourth undifferentiated, it is graded 1; if the differentiated and undifferentiated epithelium are about equal it is graded 2; if the undifferentiated epithelium forms about three-fourths and the differentiated about one-fourth of the

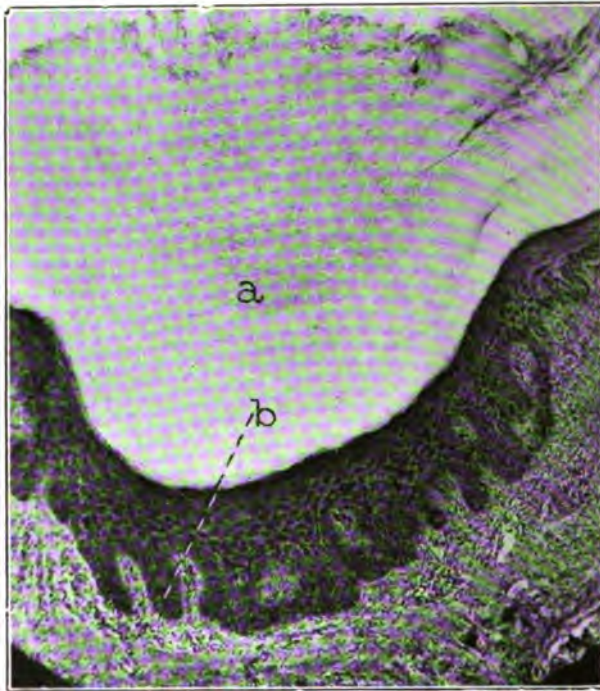


FIG. 308.—(a21283). Marked leukoplakia of the lip, characterized by increase of a, horny layer of epidermis; b, basal layer.

growth it is graded 3; if there is no tendency of the cells to differentiate it is graded 4. Of course the number of mitotic figures and the number of cells with single large deeply staining nucleoli (one-eyed cells) play an important part in the grading.

Some epitheliomas of the lip are very active and from the start show little or no tendency to differentiate; some grow more malignant with time; and others increase in malignancy and then retrogress. Unquestionably an epithelioma of a low grade of malignancy is made more

malignant by irritation with chemicals such as hydrochloric or nitric acid, silver nitrate, or arsenic paste.

Chronic ulcers of the lip, like chronic ulcers of the stomach, should be examined very closely for cancer, provided syphilis has been eliminated. MacCarty has demonstrated early cancer in the epithelium at or near the edge of gastric ulcers; practically the same process is found in early cancer on ulcer of the lip. In the lip the cancer starts

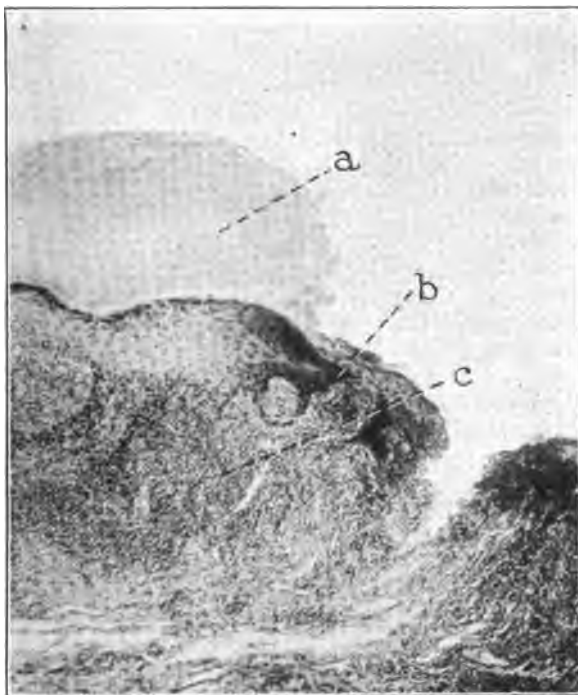


FIG. 309.—(a152243). Ulcer associated with a leukoplakia of the lip; a, leukoplakia; b, junction of epidermis and ulcerated area; c, lymphocytes.

in the stratum germinativum of the epidermis at or near the border of the ulcer. Not all cancers of the lip are preceded by ulcers but the majority are.

I shall present the facts in statistical form and make the deductions, not from one, but from various standpoints: (1) the duration and size of lesion; (2) the use or non-use of tobacco; (3) the use or non-use of caustics, pastes or plasters; and so forth, before treatment at the clinic; (4) metastasis or no metastasis; (5) cellular activity; and (6) other points of general interest.



TABLE 1.—SQUAMOUS-CELL EPITHELIOMA OF THE LIP: 537 CASES  
26.85 per cent of 2000 cases of general epithelioma

	Per cent
Patients.....	537
Males.....	526 (97.95)
Females.....	11 ( 2.05)
Age:	
Youngest patient.....	21
Oldest patient.....	97
Average age of patients.....	57.3
Occupation:	
	Per cent
Farmer.....	56.7
Laborer.....	9.0
Merchant.....	3.83
Traveling salesman.....	2.87
Railroad employee.....	2.87
Carpenter.....	2.68
Lawyer.....	1.34
Blacksmith.....	1.15
Clerk.....	1.15
Other occupations 59, each below 1 per cent.....	18.4
Family history of malignancy.....	14.9
Previous lesion at site of cancer:	
Sore or ulcer (coldsore 10.6 per cent).....	63.3
Crack.....	4.1
Leukoplakia.....	3.7
Tobacco:	
Patients using tobacco.....	80.49
Patients not using tobacco.....	19.51
Females using tobacco (smoke).....	45.45
Females not using tobacco.....	45.45
Methods of using tobacco:	
Patients who smoke only.....	69.82
Patients who chew only.....	6.31
Patients who smoke and chew.....	23.5
Patients who use snuff.....	0.35
Total number of smokers.....	93.33
Total number of chewers.....	29.82
Total number of snuffers.....	0.35
Methods of smoking:	
Pipe only.....	40.69
Cigars only.....	19.18
Pipe and other methods and with chewing.....	37.79
Cigars with other methods and with chewing.....	31.97
Total number of pipe smokers.....	78.48
Total number of cigar smokers.....	51.16
Total number of cigarette smokers.....	1.16

TABLE 1.—(Continued).

History of injury .....	8.38
	Years
Average duration of lesion .....	2.58
Longest duration of lesion .....	28.00
Shortest duration of lesion .....	0.08
Greatest diameter .....	12.5
Average greatest diameter .....	2.4
	Per cent
Origin of lesion:	
Lower lip .....	95.69
Upper lip .....	3.55
Left angle of mouth .....	0.56
Right angle of mouth .....	0.18
Lower lip:	
Left lower lip .....	43.60
Right lower lip .....	38.64
Middle lower lip .....	17.75
Upper lip:	
Left upper lip .....	53.33
Right upper lip .....	33.33
Middle upper lip .....	13.33

TABLE 2.—500 MEN WITHOUT EPITHELIOMA OF THE LIP

Average age, years .....	36.07
	Per cent
Users of tobacco .....	78.6
Non-users of tobacco .....	21.4
Methods of using tobacco:	
Smoke only .....	82.95
Chew only .....	4.32
Smoke and chew .....	12.72
Snuff .....	0.20
Total number of smokers .....	95.67
Total number of chewers .....	17.04
Total number of snuffers .....	0.20
Methods of smoking:	
Pipe only .....	6.11
Cigars only .....	16.48
Cigarettes only .....	26.32
Pipe and other methods, and chewing .....	31.91
Cigars and other methods, and chewing .....	42.02
Cigarettes and other methods, and chewing .....	30.05
Total number of pipe smokers .....	38.03
Total number of cigar smokers .....	58.51
Total number of cigarette smokers .....	59.04

TABLE 3.—TREATMENT ELSEWHERE IN SQUAMOUS-CELL EPITHELIOMA OF THE LIP

	Per cent
<b>Non-surgical:</b>	
1. One or more treatments alone or in various combinations of acids, carbon dioxid, copper sulfate, electricity, mercury, paste or plaster, potassium iodid, radium, roentgen ray, scarlet red, shoemakers' wax, and silver nitrate.....	29.05
2. Paste or plaster alone or in combination with other non-surgical treatments.....	51.28
3. Caustics (acids or silver nitrate) alone or in combination with other non-surgical treatments.....	35.89
4. Roentgen ray alone or in combination with other non-surgical treatments.....	18.58
5. Paste or plaster alone or in combination with other non-surgical treatments (proportion of all epitheliomas of lip).....	14.89
6. Caustics (acids or silver nitrate) alone or in combination with other non-surgical treatments (proportion of all epitheliomas of lip).....	10.42
7. Roentgen ray alone or in combination with other non-surgical treatments (proportion of all epitheliomas of lip).....	5.4
<b>Surgical:</b>	
1. One or more operations.....	17.87
2. Excision of growth from lip without removing lymph nodes.....	53.12
3. Excision of V from lip without removing lymph nodes.....	5.2
4. Excision of growth and one or more groups of lymph nodes.....	16.66
5. Excision of V from lip and one or more groups of lymph nodes.....	6.25
6. Miscellaneous.....	18.75
<b>Surgical and Non-surgical.</b>	
1. One or more operations and one or more treatments with acids, carbon dioxid, etc., alone or in various combinations.....	4.65
2. Operations without treatment with acids, carbon dioxid, etc., before or after operation.....	13.22
3. Treatment with acids, carbon dioxid, etc., without operation.....	24.39
4. Operation and treatment with acids, carbon dioxid, etc.....	37.61

TABLE 4.—PATIENTS OPERATED ON AT THE MAYO CLINIC

Cases.....	516 (96.08 per cent of 537)
1. Excision of submental lymph nodes, submaxillary lymph nodes, and salivary glands of both sides, and V-shaped excision of epithelioma of the lip (one operation).....	203 (39.34 per cent of 516)
2. V-shaped or quadrilateral shaped excision of epithelioma of the lip.....	56 (10.85 per cent of 516)
3. Excision of submental lymph nodes, submaxillary lymph nodes, and salivary glands of both sides and quadrilateral-shaped excision of epithelioma of the lip (one operation).....	25 (4.84 per cent of 516)
4. Excision of submental lymph nodes and submaxillary lymph nodes and salivary glands on one side, and V-shaped excision of epithelioma of the lip (one operation).....	17 (3.29 per cent of 516)

TABLE 4.—(Continued).

5. Unilateral block dissection (one operation).....	15 (2.9 per cent of 516)
6. Miscellaneous (various combinations of operations, cauteries, excisions of specimens for diagnosis, at one time or at different times).....	200 (38.76 per cent of 516)

## REMOVAL OF LYMPH NODES AND SALIVARY GLANDS

Cases.....	449
1. Submental lymph nodes.....	436 (97.1 per cent of 449)
2. Submaxillary lymph nodes and salivary glands (unilateral).....	58 (12.91 per cent of 449)
3. Submaxillary lymph nodes and salivary glands (bilateral).....	378 (84.18 per cent of 449)
4. Cervical lymph nodes.....	75 (16.7 per cent of 449)
5. Block dissections (alone or combined with other operations).....	45 (10.02 per cent of 449)
6. Cases in which the lymph nodes were removed months or years after the removal of the epithelioma of the lip.	11 (2.44 per cent of 449)
7. Lymph nodes removed (one or more groups).....	449 (87.01 per cent of 516)
8. Cases in which no lymph nodes were removed.....	67 (12.98 per cent of 516)

## PATIENTS WITH INOPERABLE EPITHELIOMA

Cases.....	21 (3.9 per cent of 537)
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TABLE 5.—PATHOLOGIC FINDINGS IN CASES IN WHICH LYMPH NODES AND SUBMAXILLARY SALIVARY GLANDS WERE REMOVED

Cases.....	No. 449
No metastasis found.....	344 (76.62 per cent)
Metastasis found.....	105 (23.38 per cent)
Submaxillary lymph nodes alone (one side).....	44 (41.90 per cent)
Submaxillary lymph nodes and salivary glands (one side)...	13 (12.38 per cent)
Submaxillary lymph nodes (one side) and submental lymph nodes.....	7 (6.66 per cent)
Submaxillary lymph nodes, salivary glands, and superior... superficial cervical lymph nodes (one side).....	6 (5.71 per cent)
Submental lymph nodes alone.....	5 (4.76 per cent)
Submaxillary lymph and superficial cervical lymph nodes (one side).....	6 (5.71 per cent)
Submaxillary lymph nodes (both sides) and submental lymph nodes.....	5 (4.76 per cent)
Submaxillary lymph nodes (both sides), submental and anterior jugular lymph nodes (one side).....	3 (2.85 per cent)
Miscellaneous (submaxillary lymph nodes and salivary glands, submental, cervical, parotid, supraclavicular and peribronchial lymph nodes; lung and liver, alone or in various combinations).....	16 (15.23 per cent)
Submaxillary lymph nodes, total involvement.....	92 (87.61 per cent)
Submaxillary salivary glands, total involvement.....	23 (21.90 per cent)

TABLE 5.—(Continued).

Submental lymph nodes, total involvement.....	26 (24.76 per cent)
Cervical lymph nodes (one or more groups).....	26 (24.76 per cent)
Superior deep cervical nodes.....	3 (7.89 per cent)
Inferior deep cervical nodes.....	3 (7.89 per cent)
Exterior jugular nodes.....	24 (63.15 per cent)
Anterior cervical nodes.....	8 (21.05 per cent)
Supraclavicular nodes, total involvement.....	1 ( 0.95 per cent)
Parotid lymph nodes, total involvement.....	1 ( 0.95 per cent)
Peribronchial nodes, total involvement.....	2 ( 1.90 per cent)
Lung, total involvement.....	1 ( 0.95 per cent)
Liver, total involvement.....	1 ( 0.95 per cent)
Submaxillary lymph nodes, total involvement on both sides.....	13 (12.38 per cent)
Cervical nodes, total involvement on both sides.....	2 ( 1.90 per cent)

TABLE 6.—GRADE OF 537 CASES ON A BASIS OF 1 TO 4 ACCORDING TO CELLULAR ACTIVITY

	Cases	Per cent
Grade 1.....	85	15.82
Grade 2.....	333	62.01
Grade 3.....	113	21.04
Grade 4.....	6	1.11

## DURATION AND SIZE OF EPITHELIOMA ACCORDING TO GRADE

	Grade 1	Grade 2	Grade 3	Grade 4
Longest duration.....	10.00 years	25.00 years	28.00 years	2.00 years
Shortest duration.....	0.10 years	0.08 years	0.08 years	0.91 years
Average duration.....	1.43 years	2.77 years	3.33 years	1.29 years
Largest size.....	5.00 cm.	10.00 cm.	7.50 cm.	2.00 cm.
Smallest size.....	0.20 cm.	0.30 cm.	0.20 cm.	1.80 cm.
Average size.....	1.23 cm.	2.28 cm.	3.25 cm.	1.90 cm.

## EPITHELIOMA PRECEDED BY ULCER

	Cases
Grade 1.....	52 (15.29 per cent)
Grade 2.....	225 (66.17 per cent)
Grade 3.....	60 (17.64 per cent)
Grade 4.....	3 ( 0.88 per cent)

## PROPORTION OF EACH GRADE PRECEDED BY ULCER

Grade 1.....	61.17 per cent of 85
Grade 2.....	67.56 per cent of 333
Grade 3.....	53.09 per cent of 113
Grade 4.....	50.00 per cent of 6

## INOPERABLE EPITHELIOMA ACCORDING TO GRADE

Grade 1	Grade 2	Grade 3	Grade 4
0	12	7	2

TABLE 7.—RESULTS

## GENERAL ULTIMATE RESULTS

Patients traced (operable 306; inoperable 8).....	314 (58.47 per cent of total)
Patients operated on.....	306
Patients dead.....	124 (40.52 per cent)
Patients alive.....	182 (59.47 per cent)
Good result (no recurrence).....	169 (92.85 per cent of 182)
Fair result (slight recurrence).....	11 ( 6.04 per cent of 182)
Bad result (no improvement).....	2 ( 1.09 per cent of 182)

## DURATION OF LIFE SINCE LAST OR ONLY OPERATION ACCORDING TO RESULT

	Good	Fair	Bad
Longest.....	14.39 years	13.68 years	2.80 years
Shortest.....	1.25 years	0.96 years	0.49 years
Average.....	7.76 years	6.8 years	1.65 years

## MORTALITY

Deaths.....	132 (42.05 per cent of 314)
Deaths of patients with operable epithelioma.....	124 (93.93 per cent of 132)
Deaths of patients with inoperable epithelioma...	8 ( 6.06 per cent of 132)

CAUSE OF DEATH OF PATIENTS OPERATED ON: DATA FROM RELATIVE, HOME PHYSICIAN,  
OR PATHOLOGIC RECORDS OF THE CLINIC

	No.
Known cause.....	99
Cancer of the lip.....	63 (63.63 per cent)
Heart disease.....	5 ( 5.05 per cent)
Nephritis.....	5 ( 5.05 per cent)
Pneumonia.....	4 ( 4.04 per cent)
Stomach trouble.....	3 ( 3.03 per cent)
Paralysis.....	3 ( 3.03 per cent)
"Following operation elsewhere".....	3 ( 3.03 per cent)
Fall.....	2 ( 2.02 per cent)
Carcinoma of the stomach.....	1 ( 1.01 per cent)
Tumor of the stomach.....	1 ( 1.01 per cent)
Abdominal tumor.....	1 ( 1.01 per cent)
Diabetes.....	1 ( 1.01 per cent)
Carcinoma of the sigmoid.....	1 ( 1.01 per cent)
Sepsis.....	1 ( 1.01 per cent)
Tuberculosis.....	1 ( 1.01 per cent)
Hepatic disease.....	1 ( 1.01 per cent)
Cardiac and hepatic disease.....	1 ( 1.01 per cent)
Sarcoma of the liver.....	1 ( 1.01 per cent)
Lung trouble.....	1 ( 1.01 per cent)
Unknown.....	25

## CAUSE OF DEATH OF PATIENTS WHO DIED IN THE MAYO CLINIC (ALL OPERABLE)

Chronic nephritis and arteriosclerosis (more than 2 years after operation).....	1
Epithelioma and abscess of the neck (52 days after operation).....	1
Epithelioma (25 days and 4 months respectively after operation).....	2
Pneumonia (few days after operation).....	3
Sepsis (12 days after operation).....	1
Total.....	8 (1.55 per cent of 516)
Actual operative mortality.....	4 (0.77 per cent of 516)

TABLE 8.—TOBACCO USERS OPERATED ON

	Grade 1	Grade 2	Grade 3	Grade 4
Number of patients.....	37	118	37	8
Patients living.....	34 (91.81 per cent of 37)	92 (77.96 per cent of 118)	10 (27.02 per cent of 37)	
Patients living, good result.....	33 (97.05 per cent of 34)	85 (92.39 per cent of 92)	10 (100 per cent of 10)	
Patients living, fair result.....	1 (2.94 per cent of 34)	6 (6.52 per cent of 92)		
Patients living, poor result.....		1 (1.08 per cent of 92)		
Patients dead.....	3 (8.10 per cent of 37)	26 (22.63 per cent of 118)	27 (72.97 per cent of 37)	3 (100 per cent of 3)
Cause unknown.....		6	5	1
Good result.....	2 (66.66 per cent of 3)	6 (30.00 per cent of 20)	7 (31.81 per cent of 22)	
Fair result.....	1 (33.33 per cent of 3)			
Poor result.....		14 (80.00 per cent of 20)	15 (68.18 per cent of 22)	2 (100 per cent of 2)
Total good result-(patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause).....				78.14 per cent
Total fair result (patient living with slight recurrence or died from other cause).....				4.37 per cent
Total poor result (patient living with no improvement or died from epithelioma).....				17.48 per cent

TABLE 9.—NON-USERS OF TOBACCO OPERATED ON

	Grade 1	Grade 2	Grade 3	Grade 4
Number of patients.....	7	37	7	
Patients living.....	6 (85.71 per cent of 7)	29 (78.37 per cent of 37)	4 (57.14 per cent of 7)	
Patients living, good result.....	6 (100 per cent of 6)	29 (100 per cent of 29)	2 (50.00 per cent of 4)	
Patients living, fair result.....			2 (50.00 per cent of 4)	
Patients dead.....	1 (14.28 per cent of 7)	8 (21.62 per cent of 37)	3 (42.85 per cent of 7)	
Cause unknown.....		1		
Good result.....	1 (100 per cent of 1)	5 (71.42 per cent of 7)		
Poor result.....		2 (28.57 per cent of 7)	3 (100 per cent of 3)	
Total good result (patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause).....				86.00 per cent
Total fair result (patient living with slight recurrence).....				4.00 per cent
Total poor result (patient died from epithelioma).....				10.00 per cent



TABLE 10.—PATIENTS OPERATED ON TREATED WITH PASTES, PLASTERS, ACIDS, AND SO FORTH, BEFORE ENTERING THE CLINIC

	Grade 1	Grade 2	Grade 3	Grade 4
Information received concerning.....				94
Patients living.....				50 (53.19 per cent of 94)
Patients living, good result.....	5 (11.11 per cent of 45)	34 (75.55 per cent of 45)	6 (13.33 per cent of 45)	
Patients living, fair result.....		1 (33.33 per cent of 3)	2 (66.66 per cent of 3)	
Patients living, poor result.....		1 (50.00 per cent of 2)	1 (50.00 per cent of 2)	
Patients dead.....				44 (46.80 per cent of 94)
Cause unknown.....		4	3	
Good result.....		5 (55.55 per cent of 9)	4 (44.44 per cent of 9)	
Poor result.....		9 (92.14 per cent of 28)	16 (57.14 per cent of 28)	
Total good result (patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause).....				62.06 per cent of 87
Total fair result (patient living with slight recurrence).....				3.44 per cent of 87
Total poor result (patient living with no improvement or died from epithelioma).....				34.48 per cent of 87

TABLE 11.—PATIENTS OPERATED ON NOT TREATED WITH PASTES, PLASTERS, ACIDS, AND SO FORTH, BEFORE ENTERING THE CLINIC

Information received concerning.....	Grade 1	Grade 2	Grade 3	Grade 4	212
Patients living.....					131 (61.79 per cent of 212)
Patients living, good result....	34 (27.64 per cent of 123)	83 (67.47 per cent of 123)	6 (4.87 per cent of 123)		
Patients living, fair result....	1 (12.50 per cent of 8)	7 (87.50 per cent of 8)			
Patients dead.....					
Cause unknown.....		10	9		81 (38.20 per cent of 212)
Good result.....	4 (16.00 per cent of 25)	17 (68.00 per cent of 25)	4 (16.00 per cent of 25)		1
Fair result.....	1 (100 per cent of 1)				
Poor result.....		18 (51.30 per cent of 35)	17 (48.45 per cent of 35)		
Total good result (patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause).....					77.08 per cent of 192
Total fair result (patient living with slight recurrence or died from other cause).....					4.68 per cent of 192
Total poor result (patient died from epithelioma).....					18.22 per cent of 192

TABLE 12.—PATIENTS WITH METASTASIS OPERATED ON

No information received concerning.....	36 (34.29 per cent of 105)
Information received concerning.....	69 (65.71 per cent of 105)
Patients living.....	12 (17.39 per cent of 69)

	Grade 1	Grade 2	Grade 3
Patients living, good result*.....		5 (50 per cent of 10)	5 ( 50 per cent of 10)
Patients living, fair result*.....			1 (100 per cent of 1)
Patients living, poor result*.....			1 (100 per cent of 1)
Total number of good results.....			10 (83.33 per cent of 12)

## DURATION OF LIFE OF PATIENTS WITH GOOD RESULT FROM LAST OR ONLY OPERATION

Longest.....	11.73 years		
Shortest.....	3.29 years		
Average.....	6.18 years		
Patients dead.....	57 (82.6 per cent of 69)		
Grade 1	Grade 2	Grade 3	Grade 4
0	15 (34.09 per cent of 44)	26 (59.09 per cent of 44)	3 (6.81 per cent of 44)

Longest duration of life from last or only operation of patients who died from epithelioma.....	2.5 years
Shortest duration of life from last or only operation of patients who died from epithelioma.....	0.066 years
Average duration of life from last on only operation of patients who died from epithelioma.....	0.79 years
Longest duration of life from last or only operation of patients who died from epithelioma or other cause.....	4.88 years
Shortest duration of life from last or only operation of patients who died from epithelioma or other cause.....	0.016 years
Average duration of life from last or only operation of patients who died from epithelioma or other cause.....	0.86 years

TABLE 12—(Continued)

CAUSE OF DEATH	
Epithelioma.....	44 (91.66 per cent of 48)
Lung trouble.....	1 (2.08 per cent of 48)
Sepsis.....	1 (2.08 per cent of 48)
Heart disease.....	1 (2.08 per cent of 48)
Pneumonia.....	1 (2.08 per cent of 48)
Not stated.....	9

\* In the 10 patients with metastasis who reported a good result, and in the one who reported a fair result, the submaxillary lymph nodes on one side only were involved. In the one patient who reported a poor result, the submaxillary lymph nodes and the salivary gland on one side only were involved.

TABLE 13.—PATIENTS WITH METASTASIS IN SUBMAXILLARY LYMPH NODES ON ONE SIDE ONLY

No information received concerning.....	14 (30.81 per cent of 44)
Information received concerning.....	30 (69.18 per cent of 44)
Patients living.....	11
Patients living, good result.....	10 (90.9 per cent of 11)
Patients living, fair result.....	1 (9.09 per cent of 11)
Patients dead.....	19
Patients dead from epithelioma.....	14 (82.35 per cent of 17)
Patients dead from other cause.....	3 (17.64 per cent of 17)
Patients dead from cause not stated.....	2

TABLE 14.—PATIENTS WITHOUT METASTASIS OPERATED ON

	Grade 1	Grade 2	Grade 3	
No information received concerning.....				146
Information received concerning.....				198
Patients living.....				151 (76.26 per cent of 198)
Patients living, good result....	35 (25.00 per cent of 140)	99 (70.71 per cent of 140)	6 (4.28 per cent of 140)	
Patients living, fair result....	1 (10.00 per cent of 10)	8 (80.00 per cent of 10)	1 (10.00 per cent of 10)	
Patients living, poor result....		1 (100 per cent of 1)		
Total number of good results.....				140 (92.71 per cent of 151)
Patients dead.....				47 (23.73 per cent of 198)
Cause unknown.....		10		
Good result.....	3 (12.50 per cent of 24)	18 (75.00 per cent of 24)	3 (12.50 per cent of 24)	
Fair result.....	1 (100 per cent of 1)			
Poor result.....		9 (75.00 per cent of 12)	3 (25.00 per cent of 12)	
Total good result (patient recovered from epithelioma and is living or recovered from epithelioma and died from other cause).....				164 (87.23 per cent of 188)
Total fair result (patient living with slight recurrence or died from other cause).....				11 (5.85 per cent of 188)
Total poor result (patient living with no improvement or died from epithelioma).....				13 (6.91 per cent of 188)

TABLE 15.—PATIENTS WITH AND WITHOUT METASTASIS OPERATED ON

	Grade 1	Grade 2	Grade 3	Grade 4
Patients with metastasis.....	39 (97.14 per cent of 105)	63 (60.60 per cent of 105)	3 (2.85 per cent of 105)	
Patients without metastasis..	67 (19.47 per cent of 344)	248 (72.09 per cent of 344)	29 (8.43 per cent of 344)	

DURATION OF LESION BEFORE EXAMINATION AT THE CLINIC

Longest duration (patient with metastasis).....	28.00 years	Patient without metastasis.....	25.00 years
Shortest duration (patient with metastasis).....	0.16 years	Patient without metastasis.....	0.08 years
Average duration (patient with metastasis).....	3.27 years	Patient without metastasis.....	2.40 years

SIZE OF LESION AT THE TIME OF EXAMINATION AT THE CLINIC

Largest size (patient with metastasis).....	12.50 cm.	Patient without metastasis.....	10.00 cm.
Smallest size (patient with metastasis).....	1.00 cm.	Patient without metastasis.....	0.20 cm.
Average size (patient with metastasis).....	3.74 cm.	Patient without metastasis.....	2.01 cm.

ASSOCIATION OF EPITHELIOMA OF THE LIP WITH OTHER MALIGNANT NEOPLASMS

	Cases
Non-melanotic melano-epithelioma on shoulder....	1
Squamous-cell epithelioma of cheek.....	1
Squamous-cell epithelioma of bladder.....	1
Basal-cell epithelioma of eyelid.....	1
Adenocarcinoma of signoid.....	1
	5 (0.93 per cent of 537)

TABLE 16.—DURATION OF LIFE AFTER OPERATION OF PATIENTS WITHOUT METASTASIS ACCORDING TO GRADE

Good Result	Grade 1	Grade 2	Grade 3
Number of patients.....	35	98	6
Longest duration.....	14.39 years	14.31 years	12.22 years
Shortest duration.....	1.73 years	1.25 years	4.30 years
Average duration.....	7.59 years	7.54 years	7.17 years
Fair Result			
Number of patients.....	1	8	1
Longest duration.....	4.39 years	13.68 years	7.32 years
Shortest duration.....		0.96 years	
Average duration.....		7.54 years	

## DURATION OF LIFE OF PATIENTS OF ALL GRADES

	Good result	Fair result
Longest duration.....	14.39 years	13.68 years
Shortest duration.....	1.25 years	0.96 years
Average duration.....	7.53 years	7.20 years

## DURATION OF LIFE AFTER OPERATION OF PATIENTS WITHOUT METASTASIS WHO ARE DEAD

Good Result. Patients did not die from epithelioma		
Number of patients.....	3	18
Longest duration.....	5.8 years	10.19 years
Shortest duration.....	3.5 years	0.36 years
Average duration.....	4.23 years	4.24 years
		3
		9.30 years
		2.02 years
		6.07 years

TABLE 16.—(Continued)

Fair Result. Patients did not die from epithelioma but had slight recurrence			
Number of patients.....	1		
Longest duration.....	6.93 years		
Poor Result. Patients died from epithelioma			
Number of patients.....	9	3	
Longest duration.....	4.51 years	1.52 years	
Shortest duration.....	1.00 years	0.51 years	
Average duration.....	2.15 years	0.95 years	
DURATION OF LIFE AFTER OPERATION OF PATIENTS OF ALL GRADES			
	Good result	Fair result	Poor result
Longest duration.....	10.19 year		4.51 years
Shortest duration.....	0.36 years		0.51 years
Average duration.....	4.47 years	6.73 years	1.85 years
DURATION OF LIFE AFTER OPERATION OF ALL PATIENTS WITHOUT METASTASIS			
Longest duration.....	10.19 years		
Shortest duration.....	0.36 years		
Average duration.....	3.68 years		



TABLE 17.—RESULTS FOLLOWING OPERATION ACCORDING TO GRADE

	Grade 1		Grade 2		Grade 3		Grade 4	
Information received concerning								
Patients operated on.....	45	(52.94 per cent of 85)	192	(59.81 per cent of 383)	65	(62.26 per cent of 113)	4	(100 per cent of 4)
Patients living.....	40	(88.88 per cent of 45)	128	(66.66 per cent of 192)	16	(24.60 per cent of 65)		
Patients living, good result.....	39	(97.50 per cent of 40)	119	(92.96 per cent of 128)	13	(81.25 per cent of 16)		
Patients living, fair result.....	1	(2.5 per cent of 40)	8	(6.25 per cent of 128)	2	(12.50 per cent of 16)		
Patients living, poor result.....			1	(0.78 per cent of 128)	1	(6.25 per cent of 16)		
Patients dead.....	5	(11.12 per cent of 45)	64	(33.33 per cent of 192)	49	(75.38 per cent of 113)	4	(100 per cent of 4)
Good result.....	4	(80.00 per cent of 5)	23	(45.09 per cent of 51)	6	(15.78 per cent of 38)		
Fair result.....	1	(20.00 per cent of 5)						
Poor result.....			28	(54.90 per cent of 51)	32	(84.21 per cent of 38)	4	(100 per cent of 4)
Not stated.....			13		11			
Total good result (patient re-								
covered from epithelioma and								
is living or recovered from								
epithelioma and died from								
other cause).....	43	(95.55 per cent of 45)	142	(79.32 per cent of 179)	19	(35.18 per cent of 54)		
Total fair result (patient living								
with slight recurrence or died								
with other cause).....	2	(4.45 per cent of 45)	8	(4.46 per cent of 179)	2	(3.70 per cent of 54)		
Total poor result (patient living								
with no improvement or died								
from epithelioma).....			29	(16.20 per cent of 179)	33	(61.11 per cent of 54)	4	(100 per cent of 4)
Total result not stated.....			13		11			

## CONCLUSIONS

1. The 537 cases of squamous-cell epithelioma of the lip in this series represent 26.85 per cent of 2000 cases of general epithelioma.

2. Squamous-cell epithelioma of the lip occurs more often in males than in females; the proportion is 49 to 1. It occurs in patients past middle life; their average age is 57.3 years.

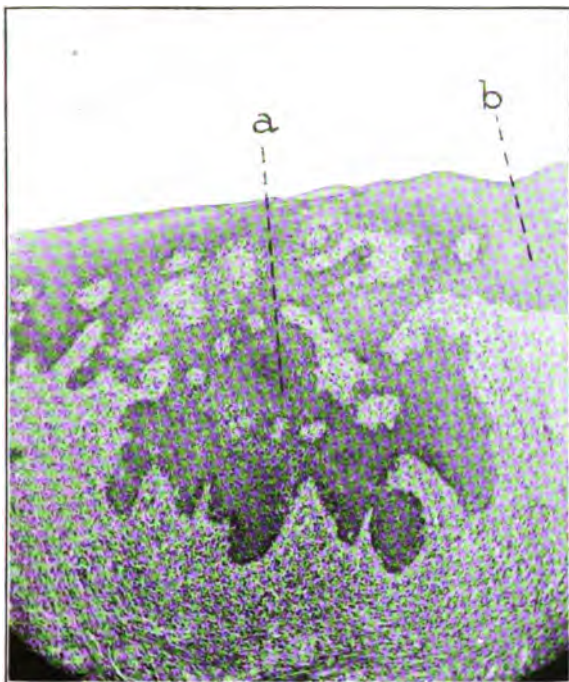


FIG. 310.—(a98158). Grade 1 epithelioma of the lip with marked differentiation; low degree of malignancy. Patient well five years after operation; a, epithelioma; b, normal epithelium.

3. The disease occurs most often in farmers; they represent 56.7 per cent of the cases.

4. A family history of malignancy plays a negligible part.

5. The site of the cancer was preceded by a sore or an ulcer in 63.3 per cent of the cases.

6. About one-fifth of all the patients do not use tobacco, while one-half of the female patients do not use it.

7. Of the patients using tobacco, 93.33 per cent smoke; 78.48 per cent of these use a pipe.

8. A comparison of 500 men without epithelioma of the lip with the 537 patients with epithelioma of the lip shows that the percentage of tobacco users and non-tobacco users is practically the same, 78.6 per cent users and 21.4 per cent non-users in the former group and 80.49 per cent users and 19.51 per cent non-users in the latter group, but that



FIG. 311.—(a64692). Grade 1 epithelioma of the lip showing marked differentiation, although it is of a slightly higher degree of malignancy than the epithelium shown in Figure 310. Patient well seven years after operation; a, completely differentiated area; b, partially differentiated cells; c, normal epithelium.

the average age of the men without epithelioma of the lip is about nineteen years less than the average age of the patients with epithelioma of the lip at the time of onset.

9. The most remarkable difference in a comparison of the patients with epithelioma of the lip and the men without epithelioma of the lip is in the method of smoking. The total number of pipe smokers in the former is 78.48 per cent and the total number of cigarette smokers is only 1.16 per cent, while in the latter the total number of pipe smokers

has dropped to 38.03 per cent and the total number of cigarette smokers has risen to 59.04 per cent.

10. A history of injury plays a negligible part.

11. The duration of the lesion shows a marked variation, from 0.08 years to 28 years, with an average of 2.58 years.

12. The greatest diameter of any lesion is 12.5 cm., the average 2.4 cm.



FIG. 312.—(a99884). Grade 2 epithelioma of the lip; not so much differentiation as in epithelioma shown in Figure 311; patient died from epithelioma of the lip four and one-half years after operation; a, completely differentiated area or pearly body; b, undifferentiated cells.

13. The lesion originated on the lower lip in 95.69 per cent of the cases, on the upper lip in 3.55 per cent, at the left angle of the mouth in 0.56 per cent, and at the right angle of the mouth in 0.18 per cent.

14. Twenty-nine and five hundredths per cent of the patients were treated with acid, paste, or plaster, and so forth, before they entered the clinic.

15. Seventeen and eighty-seven hundredths per cent of the patients were operated on before they entered the clinic.

16. Ninety-six and eight hundredths per cent of the patients were operated on at the clinic.

17. In 87.01 per cent the regional lymph nodes were removed.

18. Of the 449 cases in which the lymph nodes or salivary glands were removed, metastasis was demonstrated in 23.38 per cent; the submaxillary lymph nodes were involved in 87.61 per cent, the sub-

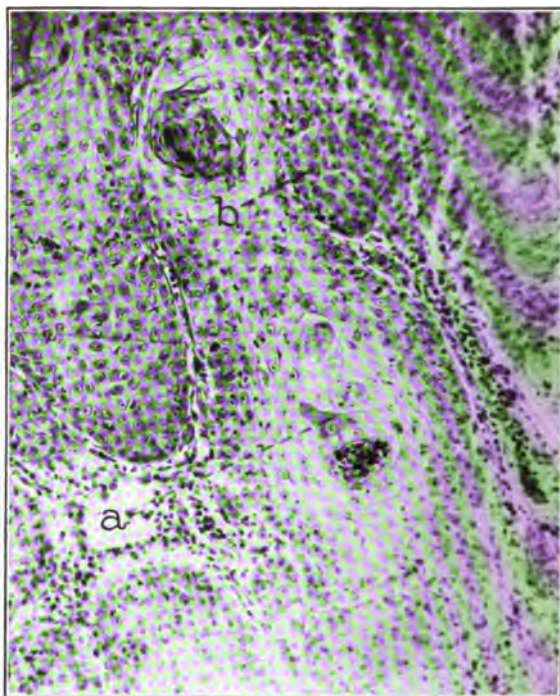


FIG. 313.—(a59017). Grade 2 epithelioma of the lip; about the same degree of malignancy as in epithelioma shown in Figure 312; patient well more than seven years after operation; a, partially differentiated cells; b, undifferentiated cells.

maxillary salivary glands in 21.90 per cent, the submental lymph nodes in 24.76 per cent, and the cervical lymph nodes in 24.76 per cent.

19. In a division of the epitheliomas according to cellular activity, on a basis of 1 to 4, Grade 1 represents 15.82 per cent, Grade 2, 62.01 per cent, Grade 3, 21.04 per cent and Grade 4, 1.11 per cent.

20. The average duration of the lesion according to grade is longest in Grade 3, 3.33 years, and shortest in Grade 4, 1.29 years.

• 21. The average size of the lesion according to grade is largest in Grade 3 and smallest in Grade 1.

22. Of the patients operated on and traced 40.52 per cent are dead and 59.47 per cent are alive.

23. Of the living patients 92.85 per cent report a good result, having been free from the disease on an average of 7.76 years.

24. Of the patients operated on who have died, concerning whom information has been received, 63.63 per cent died from epithelioma.

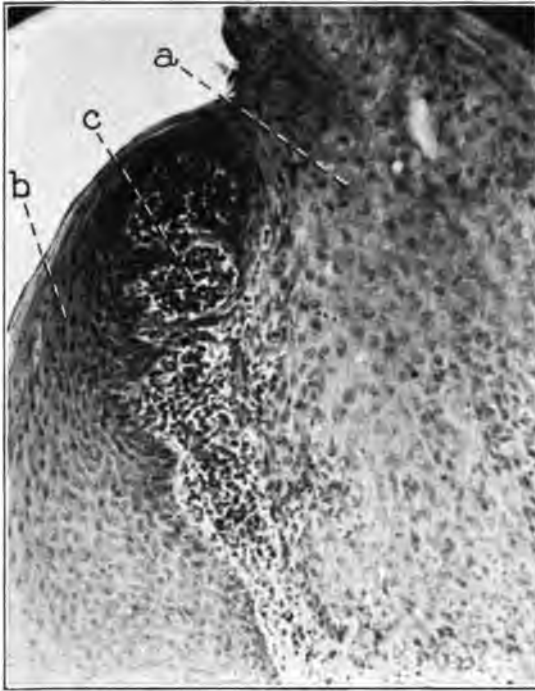


FIG. 314.—(a72479). Grade 2 epithelioma of the lip; a, epithelioma, b, normal epithelium; c, lymphocytes.

25. Eight or 1.55 per cent of the patients who were operated on died in the clinic, while the actual operative mortality was only 0.77 per cent.

26. The users of tobacco who were operated on did not obtain quite so good total good results as the non-tobacco users; 78.14 per cent in the former, and 86.0 per cent in the latter.

27. In the inoperable cases the non-tobacco users reached as high as 30.76 per cent.

28. The patients who were treated with pastes, plasters, and so forth, before entering the clinic did not obtain such good total good results as those who were not so treated, 62.06 per cent in the former and



77.08 per cent in the latter; moreover, 31.91 per cent of the former who were operated on had metastasis while only 19.48 per cent of the latter operated on had metastasis.

29. Of the patients with metastasis 17.39 per cent are living and 82.6 per cent are dead.

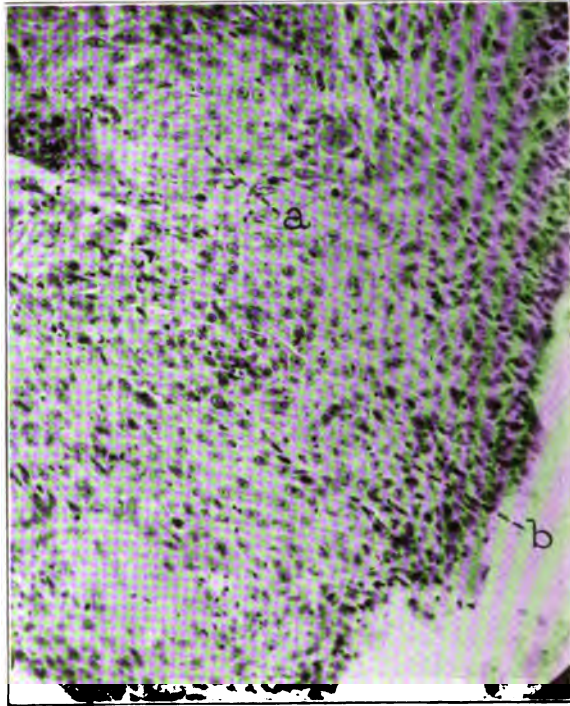


FIG. 315.—(a38260). Grade 3 epithelioma of one of the left submaxillary lymph nodes, secondary to epithelioma of the lip; slight differentiation; the patient died from epithelioma five months after the last operation and twenty months after the onset of the disease; (a) partially differentiated cells; (b) undifferentiated cells.

30. Of the living who had metastasis 83.33 per cent report a good result. In these patients the submaxillary lymph nodes on only one side were involved.

31. No patient with the cervical nodes or more than one group of any lymph nodes involved has been reported living.

32. Of the patients reported dead who had metastasis 91.66 per cent died from epithelioma.

33. If a patient has the submaxillary lymph nodes on one side only involved he has a 1 to 3 chance of getting a good result and will be living and well on an average of 6.18 years after operation.

34. Of the patients operated on in whom no metastasis was demonstrated 76.26 per cent are living, and 23.73 per cent are dead; of the living 92.71 per cent report a good result.

35. The average duration of the lesion in the patients with metastasis is 3.27 years as compared with 2.40 years in those without metastasis;

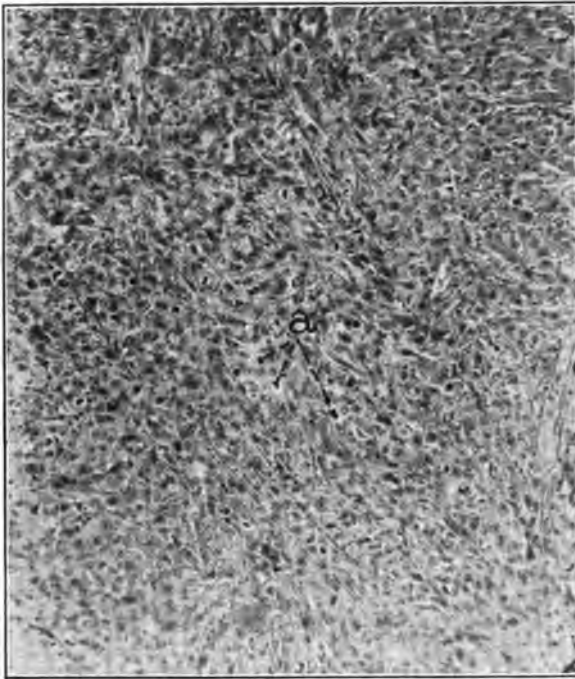


FIG. 316.—(a74162). Grade 4 epithelioma of the liver secondary to epithelioma of the right side of the upper lip. No differentiation; numerous mitotic figures; high degree of malignancy. The patient died four and one-half months after the last operation and eleven months after the onset of the disease with metastatic epithelioma of the lymph nodes of the right side of the neck, right peritracheobronchial nodes, right lung, and liver; (a) mitotic figures.

the average size of the lesion is 3.74 cm. in the patients with metastasis as compared with 2.01 cm. in those without metastasis.

36. Among the known causes of death, deaths from epithelioma were as follows: none in Grade 1; 54.90 per cent of Grade 2; 84.21 per cent of Grade 3; and 100 per cent of Grade 4.

37. Some malignant neoplasm was associated with the epithelioma of the lip in 0.93 per cent of the patients.

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# ANKYLOSIS OF THE JAW DUE TO FIXATION OF THE TEMPORAL MUSCLE

## Method of Treatment\*

G. B. NEW

It is sometimes difficult to determine definitely the side involved and the location of the fixation of an ankylosis of the jaw. This is particularly true in cases in which the jaws are fully formed before the ankylosis has occurred and in which there is no deformity. The diagnosis of the location is not so difficult when the fixation has occurred early in life, causing the deformity typical of such cases.

Ankylosis of the jaw may be said to be of three types: (1) articular ankylosis, the most common type, due to the involvement of the temporomaxillary joint, (2) extra-articular ankylosis, in which the extra-articular structures or muscles are the cause, and (3) articular-extra-articular ankylosis, in which both the joint and the extra-articular structures are at fault. The clinical points of value in determining the side involved and the location of the ankylosis have been brought out in a recent article.<sup>1</sup>

The treatment of the articular type of ankylosis gives uniformly good results. It consists of an arthroplasty of the temporomaxillary joint through a curved incision 2 inches long, extending above the zygoma and down in front of the ear, and the removal of at least one-half inch of the condyle and the ascending ramus of the jaw. It is not necessary to interpose any tissue in the new joint. When the jaw is not deformed, the operation is not difficult. If the typical deformity of ankylosis developed early in life is present, the joint will be very low and should be attacked from above by removing the lower margin of the zygoma. In this way the facial nerve is avoided, which is liable to injury if care is not taken in making the dissection in the soft tissues.

\* Reprinted from Jour. Am. Med. Assn., 1919, lxxiii, 264-265.

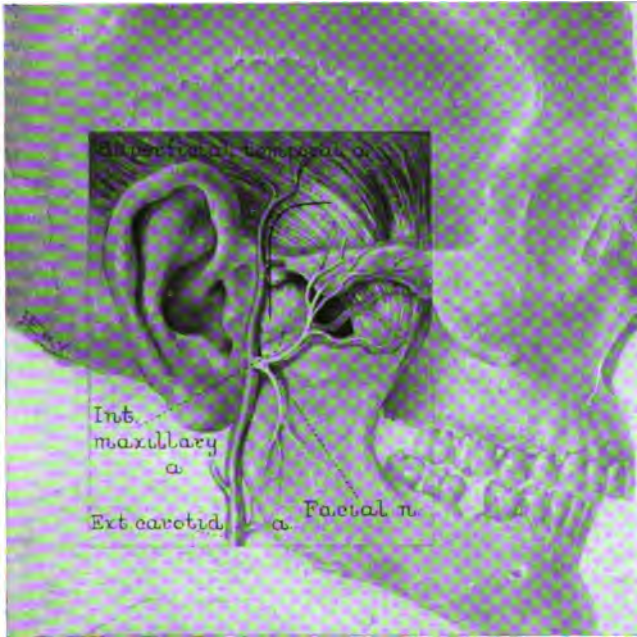


FIG. 317.—The superficial temporal artery, internal maxillary artery, facial nerve, and the location of the incision.

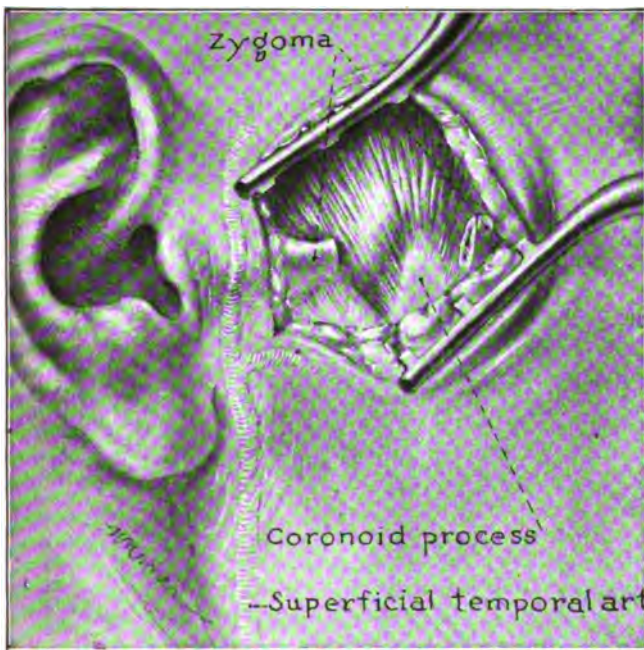


FIG. 318.—Appearance after removal of a portion of the zygoma and exposure of the coronoid process, and the attachment of the temporal muscle.

The treatment of the extra-articular and the articular-extra-articular types of ankylosis are much more difficult and present many problems. A recent case of extra-articular ankylosis of the jaw, due to fixation of the temporal muscle, suggested a method of treatment which, so far as I know, is new for this type of case.



FIG. 319.—Appearance after removal of the coronoid process along with the attachment of the temporal muscle.

#### REPORT OF CASE

(Case 118426). N. A. B., a farmer, aged 36, came to the clinic, Jan. 8, 1919, on account of inability to open his mouth. This trouble followed a gasserian ganglion operation here three and one-half years ago. The operation had been done by Dr. E. H. Beckman for trifacial neuralgia of several years' standing. The notes of the operation, July 21, 1915, follow:

"The operation was done in two stages. The Cushing incision was made, and large tortuous vessels were found throughout the entire dura. Because of the severe hemorrhage it was thought best to divide the operation into two stages and a gauze pack was inserted to be left in place for twenty-four hours. July 29, 1915, the second stage operation was done. The posterior root was evulsed and most of the ganglion removed. The bottom of the pocket was packed with gauze to control hemorrhage; the gauze was removed twenty-four hours later."

The patient made an uneventful recovery except that he was unable to open his mouth after the operation; he secured complete and permanent relief from pain.



**FIG. 320.**—(Case 118426). Complete ankylosis of the jaw due to fixation of the temporal muscle following a gasserian ganglion operation.



**FIG. 321.**—Appearance after removal of coronoid process and the attachment of the temporal muscle.

The ankylosis was complete and the patient had received no treatment for it. Except for the scar in the left temporal region extending down in front of the ear, the face was symmetrical and there was no atrophy. It was believed that the ankylosis was due to the fixation of the temporal muscle either from cutting it across at the time of the operation or from secondary inflammatory reaction. The patient was given ether, and an unsuccessful attempt was made to stretch the jaws open. In order to restore the function of the jaw, an operation was performed.

*Operation and result.*—The incision was the same as that used in the operation for arthroplasty of the temporomaxillary joint (Fig. 317). The skin and superficial tissues were incised down to the temporal fascia. A mastoid retractor was inserted and the zygoma exposed well forward. In elevating the soft tissues over the zygoma it is essential to keep close to the bone, thus preventing injury to the facial nerve. By means of blunt dissecting scissors and a periosteal elevator the inner surface of the zygoma was freed so that a piece of it 1 inch long was removed with a Gigli saw (Fig. 318). This piece was placed in a warm, wet gauze sponge. The temporal muscle and coronoid process were then exposed and removed with a curved chisel and a bone-biting forceps. The attachment of the temporal muscle to the inner surface and notch of the ascending ramus was removed by blunt dissecting scissors (Fig. 319). The temporomaxillary joint was exposed but not opened, and was found to be normal. The piece of the zygoma that had been removed was replaced and sutured by catgut sutures, and the wound closed with catgut and dermal sutures. The following day the patient could open his mouth, and in a week's time he was able to separate his teeth 1 inch. The facial nerve was not injured. He was given a screw-top mouth-gag, but he preferred to use wooden tongue depressors placed together on the flat to exercise his jaws; he could put nine of these between his teeth. He was able to chew meat or any type of food. This good function of the jaw has been maintained now for four months.

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# RETRACTING AND SUTURING OF SOFT TISSUES WITH REGARD TO THE EXTRACTION OF THE LOWER IMPACTED THIRD MOLAR\*

B. S. GARDNER

Because of the increasing interest shown by the dental profession in the use of sutures following the extraction of teeth, I am presenting



FIG. 322.—Roentgenographic picture of a typical impacted lower right third molar.



FIG. 323.—Right-angle incision through soft tissue.

In this short article, without assuming, however, that the technic is original.

It has been my experience that in order properly to close the socket of the impacted lower third molar, the operator must proceed with a definite technic with the first incision. He must have in mind that he is to attempt at least to replace the soft tissues in their original position. The steps of this technic are perhaps best described as follows:

\* Reprinted from Dental Cosmos., 1919, lxi, 1092-1093.

Figure 322 illustrates a typical impacted lower third molar. In order to gain access and to do away with a retractor, a right angled incision is first made (Fig. 323). The soft parts are then separated from the alveolar process and the resulting flap is held retracted by the

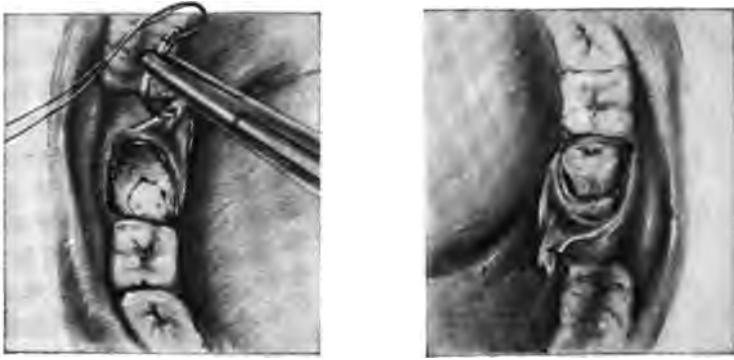


FIG. 324.—A, Soft tissue separated and right-angle flap being stitched. B, Part of osseous tissue removed and soft tissue retracted by use of one stitch.

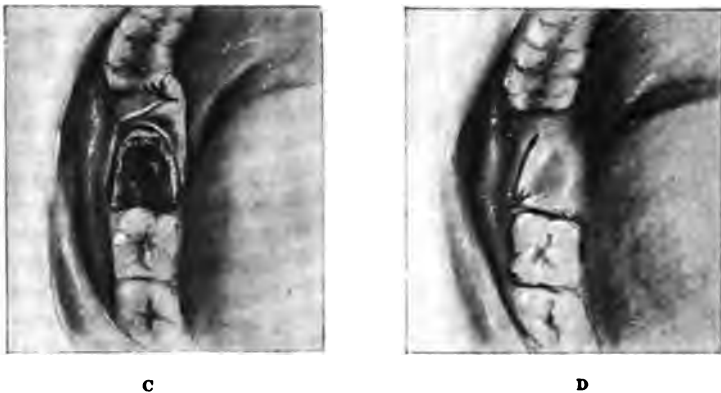


FIG. 325.—C, Impacted tooth removed. D, Soft tissue stitched in place.

use of one suture (Fig. 324). This gives the operator direct access and whatever technic is used in the osseous dissection, the flap is out of the way and is not misused.

After the removal of the tooth, and after the socket has been properly cared for, the soft parts are sutured in place (Fig. 325).

The suture of choice in this work is an especially prepared catgut known as "special exodontia suture," which resists absorption in the average mouth for from six to eight days.

## STUDIES ON ELECTIVE LOCALIZATION

### Focal Infection with Special Reference to Oral Sepsis\*

E. C. ROSENOW

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#### INTRODUCTION

That foci of infection, often insignificant and symptomless in themselves, are a cause of systemic disease is indicated by many facts. Clinical studies have shown that focal infections are present in demonstrable form in a high percentage of the sick, including children. Thorough removal of foci of infection is followed by improvement in the general health and frequently by improvement or cure of distant local and systemic diseases, provided the changes are not too far advanced. Indeed, improvement has occurred so often that many physicians have come to regard these observations as proof of etiologic relationship and, if improvement does not follow the removal of a given focus, it is considered presumptive evidence either that the particular operation was not properly performed or that other foci exist. Exacerbation of systemic conditions immediately following the removal of certain foci of infection further suggests causal relationship. The idea of an etiologic relationship is not new, and relief of systemic conditions following the removal of foci of infection is mentioned in the older medical literature.

Rush in 1801, cited by Duke, after mentioning a number of striking cures which followed extraction of diseased teeth, made the following statement: "I have been made happy by discovering that I have only added to the observations of other physicians, in pointing out a connection between the extraction of decayed and diseased teeth and the cure of general diseases." Miller in 1889 demonstrated that infection of the mouth may cause constitutional disease. Pyorrhea is mentioned as a causative factor in pathologic conditions of the joints, and tonsillitis as frequently accompanying rheumatic

\*Reprinted from Jour. Dent. Res., 1919, i, 205-268.



fever. Black emphasizes the importance of dental lesions in ocular disease and, in a review of the older medical literature, gives numerous instances indicating causal relationship between dental lesions, particularly in the form of alveolar abscess at the root apex and pus pockets along the side of the root, to diseases of the eye. The relationship between ill health and infections of the mouth was thought in earlier years to be due chiefly to the swallowing of pus and of putrid material.

Notwithstanding the repeated suggestions of etiologic relationship, the medical and dental professions, as a whole, remained indifferent until Billings<sup>2,3</sup> and his co-workers made their extensive clinical observations and correlated experimental studies in animals<sup>7,33</sup> demonstrating the importance of septic foci, even when small, as sources of chronic infections conveyed by the blood stream. The broader conception of this interrelationship, well expressed by the term "focal infection," may therefore be regarded as having had its origin in recent years. The experimental studies included dental foci as well as localized infections in other parts of the body. As early as 1908<sup>33</sup> endocarditis was produced by intravenous injection of the respective strains from a case of each staphylococcus and *Streptococcus viridans* endocarditis, which cases were clearly the result of dental infections. The combined clinical and experimental studies of Hartzell<sup>16,17</sup>, Hartzell and Henrici, Gilmer, Gilmer and Moody, and Moody, emphasized the importance of dental foci as sources of systemic infections. For a detailed consideration of results of numerous clinical and roentgenologic studies, and an exhaustive bibliography, Duke's excellent monograph on this subject should be consulted.

Experimental studies have shown that foci of infection in a given case may harbor the same type of bacteria that is found in distant lesions; that intravenous injection of the freshly isolated strains both from the focus and from the diseased organs is followed by localization and lesions in organs corresponding to those involved in the patient from whom the bacteria were isolated; and that, from the lesions produced experimentally, the organism may be isolated in pure culture, the disease again reproduced, and the organism again isolated. Moreover, immunologic evidence indicating an intimate relationship is not lacking. The bacteria having elective localizing power may be agglutinated specifically by the serum of the patient.<sup>4</sup>

In my own studies, the elective localizing power of the freshly isolated streptococci found in the focus or in systemic lesions has been demonstrated in appendicitis, ulcer of the stomach, cholecystitis, rheumatic fever,<sup>36</sup> erythema nodosum,<sup>39</sup> herpes zoster, myositis, chronic septic endocarditis,<sup>34</sup> epidemic parotitis, and acute anterior poliomyelitis.<sup>40,45</sup> A fuller discussion of these studies may be found in the writer's original papers published in the *Journal of Infectious Diseases* and the *Journal of the American Medical Association* during the past four years.

The results in ulcer have been verified in the main and extended by Helmholz<sup>19</sup> and by Hardt and those in cholecystitis by Brown. The elective localizing power of streptococci and colon bacilli from urinary infections has been demonstrated by Helmholz and Beeler.<sup>20</sup> A number of workers, on the other hand, have failed to obtain evidence of the elective localizing power of streptococci or other bacteria isolated from foci of infection, and even of strains from the infected tissues.

In my own experiments in this field, the primary consideration was to determine whether or not foci of infection harbor bacteria, quite without regard to species, which may produce the disease in animals corresponding to that found in the patient. Intensive effort was made to work with the bacteria from the depth of a focus and not merely with those on the surface which might be a saprophytic flora. Pus was expressed from tonsils, the pus in pyorrhea was aspirated from the depths of the pockets by means of a glass pipette, and studies were made on selected cases. Very early in the work it was found that the bacteria concerned were often extremely sensitive to oxygen, and that the property on which elective localization depends tended to disappear promptly, especially on aerobic cultivation. The specific strain may thus be lost even in the primary culture, unless the culture medium is particularly favorable for growth, both with regard to available nutritive material and with regard to oxygen tension. The importance of oxygen tension for the cultivation of various streptococci and the variations in this requirement for growth have been emphasized by Gräf and Wittneben, by Wherry and Oliver, and by others.

Inability to obtain evidence of the elective localizing power of bacteria in the hands of some observers, as pointed out by Gay, might well be explained by insufficient attention to technical de-

tails. Henrici,<sup>18</sup> for example, first plated his material aerobically on blood agar and then made inoculations in animals with subsutures of strains of streptococci fished from single colonies. In Moody's experiments the dose was very much smaller and the animals were allowed to live for a longer time than in my experiments. As to the general disease-producing power of streptococci and other bacteria contained in dental and other foci, however, the experimental results of all workers are more in accord. Thus, Henrici produced myositis, nephritis, myocarditis, arthritis, and arteritis, with cultures from dental foci. Moody obtained similar results.

Many facts suggest that dental infections are often metastatic from foci elsewhere than in the dental area.<sup>40</sup> The observation which I have made, that bacteria isolated from the tissues in metastatic lesions show a greater affinity for the same tissues in animals than do those isolated from the primary focus, seems to indicate that the repeated occurrence of the same type of lesion, such as pulpitis in a given case, may be the result of a blood-borne infection from one pulp to another, as well as from infection from a focus in the tonsil. The rather common occurrence of pulpitis during or following certain epidemics of acute respiratory diseases is in harmony with this idea. That infection of the pulp may be metastatic is shown by the fact that it occurs in sound teeth, that apical abscesses are sometimes found at the roots of otherwise normal teeth whose pulp chambers have not been perforated either by treatment or decay, and that infection is occasionally found in unerupted teeth. Moreover, direct experimental evidence that this may occur has been obtained. In a previous communication, I have shown the affinity for dental pulps and dental nerves, in animals, of a streptococcus isolated from the foul pulp of a tooth of a person in whom infection of a number of pulps subsequently occurred.

I shall now outline a method for a bacteriologic and experimental study applicable to dental problems, record further data concerning the localizing power of bacteria isolated from various dental foci of infection, report detailed experiments in a few illustrative cases, and present certain deductions which may serve as useful guides in various dental procedures.

#### DESCRIPTION OF THE EXPERIMENTS AND THEIR RESULTS

The solution of many dental problems will depend, to a large extent, on bacteriologic studies. The usual, although standard,

methods are not always sufficient. The methods should be adapted to the special conditions in this field. Streptococci and other bacteria in tissues and in chronic foci of infection, particularly those about teeth, are often extremely sensitive to oxygen. Many bacteria require partial oxygen tension and do not grow under strictly anaerobic or aerobic conditions.<sup>36</sup> Aerobic cultivation of those less sensitive tends to destroy the property on which elective localization depends. The amount of material obtainable for inoculation and the number of bacteria in many cases of dental infection are small, and hence particularly adaptable mediums are indicated. The method of making the primary cultures should be simple so that it can readily be applied with little annoyance to the patient and operator. A method embodying the above requirements, and similar to one I have described previously,<sup>37</sup> has proved useful in studying the bacteriology and the localizing power of the bacteria isolated in various dental infections.

#### METHOD FOR THE BACTERIOLOGIC STUDY OF DENTAL INFECTIONS

Two mediums, dextrose-brain broth and soft dextrose-brain agar, have been found especially useful. They are prepared from meat infusion or beef extract in the usual way, and titrated so that the final product is from 0.5 to 0.7 acid to phenolphthalein. In order not to interfere with the growth of sensitive bacteria and yet to indicate their number, the agar medium is made to contain only 0.5 per cent of agar, just sufficient to jelly, instead of the usual 1.5 or 2 per cent. Both of these mediums are placed in test tubes so that the column of medium is at least 8 cm. tall. Pieces of fresh brain substance, equivalent to about 1 gm., are added to the bottom of each tube to make the column approximately 10 cm. tall. The mediums are then sterilized in an autoclave at 15 pounds pressure for fifteen minutes, or in an Arnold sterilizer on three successive days. Dextrose, from a concentrated sterilized solution, is added to both mediums after sterilization to make them 0.2 per cent dextrose, also decolorized acid fuchsin (Adraid's indicator). The addition of ascites fluid, blood, or serum, just before use, while advantageous in special instances, is found unnecessary for routine work. The brain substance renders the bottom of the tube anaerobic; the top necessarily is aerobic and it follows that every gradation of oxygen pressure occurs between these two points. The

growth in these liquid mediums almost invariably begins at the bottom of the tube and then forces its way upward, in some instances to the

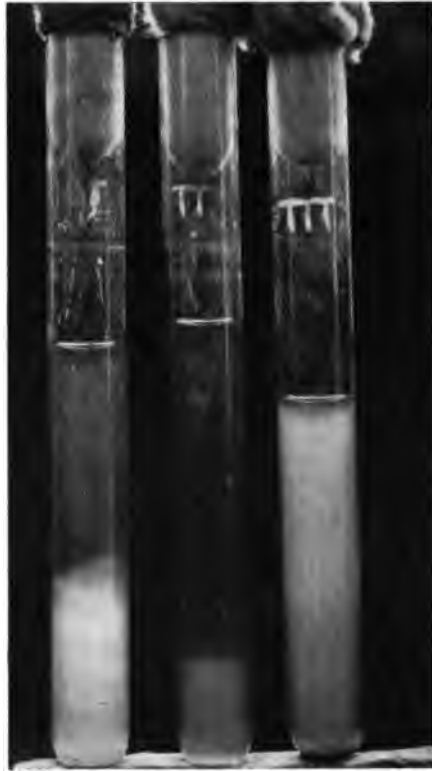


FIG. 326.—Photograph of broth cultures, illustrating the importance of the use of tall columns of mediums in connection with study of dental infections.

*Tube I.* Dextrose-acacia broth inoculated with infected pulp of tooth in a case of iritis (Case 3458).

*Tube II.* Dextrose-acacia broth inoculated with the iris of rabbit showing iritis following injection of culture from the apex of the same tooth.

*Tube III.* Dextrose-blood broth inoculated with the iris of the rabbit showing iritis.

The growths in Tubes I and II remained limited to the lower portion of the tubes for seventy-two hours; the growth in Tube III was limited to the lower portion for forty-eight hours, and then forced its way to the top during the third twenty-four hours. Aerobic blood-agar plates of Tubes I and II were negative, while III showed a pure culture of *Streptococcus viridans*.

top of the medium within twenty-four hours; in others, in forty-eight or seventy-two hours, or not at all (Fig. 326). Tall tubes of broth made

from meat infusion in the usual way, to which 5 per cent of blood is added and 0.5 per cent of dextrose from a concentrated solution just before use, have proved specially useful in studying the localizing power of bacteria from dental foci.

The liquid mediums are specially useful for studying the localizing powers of the primary culture, but they give little indication as to the number of bacteria present in the material inoculated, and one contaminating organism from the air or elsewhere may outgrow the more parasitic organisms contained in the material under consideration. The agar medium, in conjunction with a study of smears of the material inoculated, furnishes quite accurate information as to the number of bacteria contained in the material inoculated and should be used as a control of the liquid medium. In the agar medium, contaminating bacteria do not outgrow those contained in the material inoculated. The bacteria live for a long time, and the properties on which elective localization depends may be retained in the deep colonies for a longer period than when grown aerobically, so that transfers to the liquid mediums for animal injections may be made at a considerable period after growth has occurred.

The material from a foul pulp or a dental canal may be inoculated directly with a broach; effort should be made to carry some of it to the deeper layers of the mediums. A granuloma, or other material from apical infections, may be emulsified in sodium chlorid solution in a mortar in a specially devised sterile air chamber and then inoculated or it may be dropped into the broth directly. Transfers from these mediums to blood agar or other mediums may be made for identification and for other studies.

In the removal of teeth some danger of contamination with the mouth flora exists even when extreme measures are adopted for sterilizing the gum margins. This danger becomes slight in proper hands and, if the agar medium yields many colonies, one may be sure that the bacteria were contained in the material inoculated. If few bacteria exist in the tissue, as may be the case in chronic granuloma, control cultures in the agar medium, of the material contained in the pulp chamber of abscessed teeth, for example, should always be made. This may be done conveniently by sterilizing the surface of the tooth in a Bunsen flame, or by dipping it in alcohol and burning the alcohol, care being taken not to overheat the tooth and thus kill the bacteria in the pulp. If cultures can not be made immediately, the tooth should

be wrapped in dry sterile gauze; it should not be placed in sterile salt solution or other liquids as is so often done. The pulp chamber may be entered from the seared apical end with the aid of a flamed dental drill, or by splitting the tooth wrapped in sterile gauze in the jaws of a rigid vise. Moreover, the presence of bacteria is readily demonstrated by incubating the granuloma or other tissue in the depths of the medium for from eight to twelve hours, fixing the tissue in 10 per cent



FIG. 327.



FIG. 328.

FIG. 327.—Photomicrograph of small granuloma near the apex of an extracted tooth whose root canal was improperly filled five years previously. Gram-Weigert,  $\times 50$ . This specimen was obtained in a sterile manner, incubated at  $35^{\circ}\text{C}$ . for ten hours in the bottom of a tall tube of dextrose broth and then placed in 10 per cent formalin. The broth showed slight turbidity at the bottom due to streptococci. Note the dark area at *a*, near the apex of the granuloma; and the line at *b*, indicating the path of the blood vessels from this area.

FIG. 328.—Photomicrograph revealing mass of streptococci in the dark area shown at *a*, in Figure 327. Gram-Weigert,  $\times 500$ . Painstaking search in serial sections showed this mass to be the only one throughout the tissue and hence it may be taken to indicate the point where the infection existed before the tooth was extracted.

formalin, and cutting and staining sections. At the point where living bacteria occur a colony containing many bacteria is formed and, owing to the density of tissues, it is readily demonstrable microscopically. This procedure has the advantage of showing the location of the bacteria in their relation to the blood-vessels (Figs. 327 to 335).

For details regarding inoculations of animals, reference should be made to the original papers on elective localization. Suffice it to state here that inoculations in animals should be made intravenously, although specific localization has been obtained in some instances

following intraperitoneal inoculation. The culture to be injected should be mixed so that the bacteria grown at the different levels are included. Control cultures of the material injected should always be made, since the freshly isolated organisms tend to die quickly and a negative result may be due to this cause. At least two animals, preferably medium-sized rabbits, should be inoculated with a given culture, one with a relatively small dose (1 to 5 c.c.), the other with a large dose (5 to 10 c.c.). The dose in special instances may be made

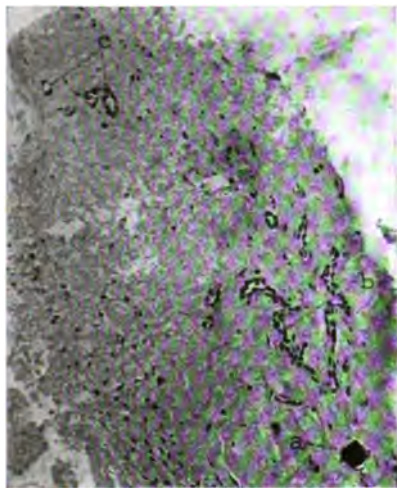


FIG. 329.

FIG. 329.—Granuloma shown in Figure 349 after incubation in dextrose-acacia broth for ten hours. Note the dark area at *a*, consisting of a capillary filled with diplococci. The capillaries are lined with a single layer of endothelium at *b* and *c*. Hematoxylin and eosin,  $\times 200$ .

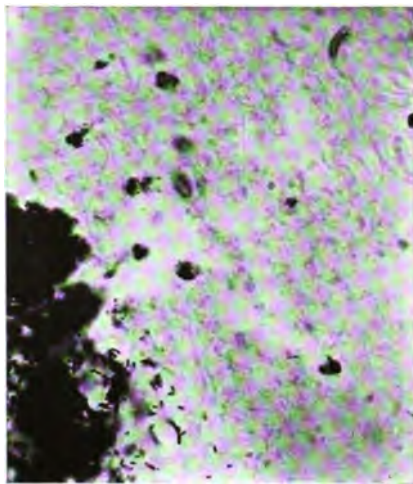


FIG. 330.

FIG. 330.—Granuloma shown in Figure 329. Note the large dark area at the left consisting of Gram-positive diplococci, and the scattered leukocytes containing diplococci. This area corresponds to the one showing newly formed capillaries at *b*, Figure 329. Gram-Weigert,  $\times 500$ .

smaller or larger, depending on the type of bacteria at hand. If the bacteria are separated from the broth and suspended in salt solution, the dose should be increased. The animal should be anesthetized in from forty-eight to seventy-two hours after injection, and examined carefully in a bright light for lesions. Animals seemingly well have frequently shown specific lesions. Repeatedly negative results have been reported by the inexperienced investigator when unmistakable lesions were found on closer examination, especially in the case of



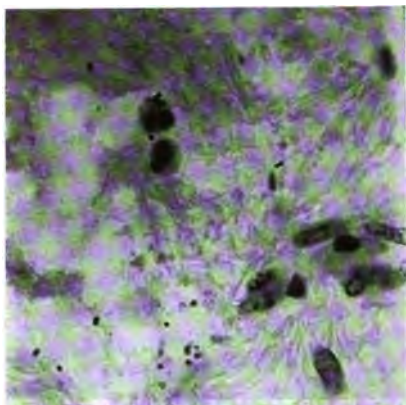


FIG. 331.

FIG. 331.—Granuloma shown in Figure 329. Note the capillary adjacent to the hemorrhagic and edematous area, containing leukocytes and diplococci. Gram-Weigert,  $\times 1000$ .

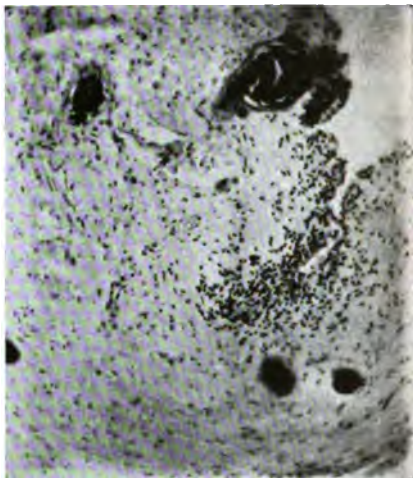


FIG. 332.

FIG. 332.—Section of the pulp of the first right upper bicuspid in Case 3368. Note the area of round-cell infiltration and the dark masses filling the blood vessels. Hematoxylin and eosin,  $\times 120$ .

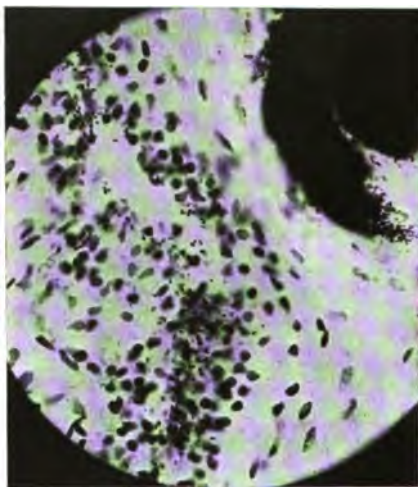


FIG. 333.

FIG. 333.—Higher magnification of the large blood vessel shown in Figure 332. Note the large number of diplococci in the blood vessel, showing branching in the adjacent infiltrated tissue. Gram-Weigert,  $\times 500$ .

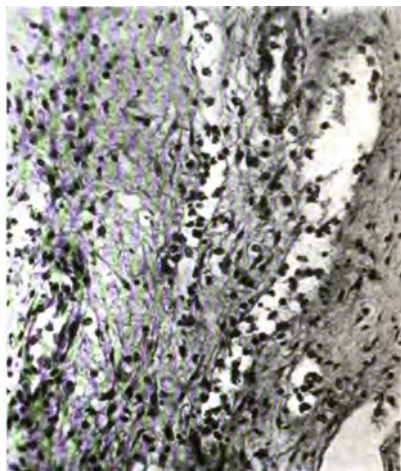


FIG. 334.

FIG. 334.—Section of the dental pulp shown in Figure 346 after incubation for ten hours in dextrose-acacia broth. Note the large number of leukocytes in and adjacent to the capillaries. Hematoxylin and eosin,  $\times 200$ .

experiments in myositis and arthritis. Cultures and sections from the lesions should, of course, be made to determine the identity of the causative organisms, especially if the primary mixed cultures are injected. The nonpathogens disappear from the circulation and the tissues with remarkable rapidity, and the specific organism quickly

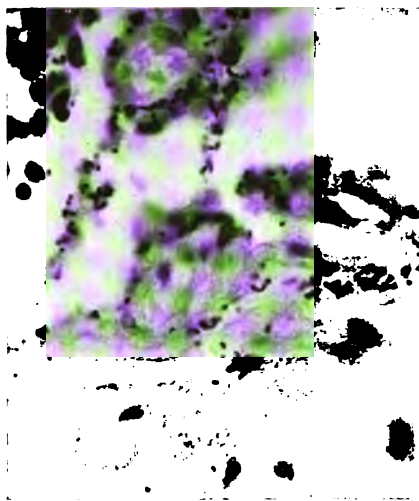


FIG. 335.—Dental pulp shown in Figure 334. Note the large number of streptococci in and adjacent to the capillary walls, and in and along the lymph channels. Gram-Weigert,  $\times 1000$ .

localizes and produces lesions. The animal often serves as an efficient plating, separating the pathogens from the nonpathogens. This fact was emphasized some years ago when it was shown that *Streptococcus viridans* from endocarditis was isolated in pure culture from lesions in the heart valves, and hemolytic streptococcus was isolated from the turbid joint fluid in animals after mixtures of the two strains had been injected intravenously.

#### LOCALIZATION OF BACTERIA FROM DENTAL FOCI OF INFECTION

In Table 1 is given a summary of results obtained in animals injected intravenously with cultures obtained from dental foci. The figures indicate the percentage incidence of lesions in various organs as revealed by necropsy. In cases in which lesions were not found blanks are left in the table, although in some instances lesions would

TABLE 1.—LOCALIZATION OF BACTERIA FROM DENTAL FOCI OF INFECTION

Diseases	Percentage of animals showing lesions in																																
	Strains (42)	Animals injected (156)	Eyes	Teeth	Skin	Lymph glands	Thyroids	Muscles	Joints	Intestines	Appendix	Stomach (hemorrhage)	Stomach (ulcer)	Duodenum (hemorrhage)	Duodenum (ulcer)	Gallbladder	Pancreas	Spleen	Adrenals	Kidneys	Bladder	Thymus	Lungs	Pericardium	Myocardium	Endocardium	Nerves	Ganglia	Meninges	Spinal cord	Br.		
Myositis and chronic arthritis	17	62	9	11	2	2	3	47	23	2		9	5		9		5	2	14			5	10	10	16	22	12					2	2
Ulcer	6	24					8	8	4			46	38	8	13	13		4				8	4										
Appendicitis	1	1									100	100																					
Neuritis	3	12					42	16	16										16	8		16	8	16	8	68	8						
Herpes zoster	4	16	13	25	19	13	6	25	31		6	6			6	6	13	13	13			25	6	6	6	39	19						6
Multiple sclerosis	5	12			8		25	17	8		8	8						17	17			8		8	8	8						18	33
Transverse myelitis	2	15					7	13		7	27		7		7			7	7											7		20	27
Goiter	3	9					44	11	33		11				11			11	11			11	11	11	22								
Keratitis and iritis	1	5	60	60	20	20	20	60	40	20	20			20					20			20											

no doubt have been found if sufficient time had been available to make a complete search. Owing to the frequency with which colon bacilli contaminate primary cultures from pyorrhea pockets, some of the cultures injected had been plated on blood agar. On analysis, this was found to be the reason for the relatively low total incidence of elective localization in some of the diseases studied. In instances in which the primary cultures were injected, the tendency to localize electively was usually well marked. Only one culture was made in each case. It was not intended to obtain a culture from the focus at any particular time, as during an exacerbation of symptoms, although cultures happened to be obtained during such periods in some instances. The table records the results obtained from injecting 151 animals with cultures from 42 cases.

The incidence of lesions in the organs or tissues in the animals, corresponding to those involved in the patient, was relatively high in myositis and dental neuritis, ulcer of the stomach, appendicitis, neuritis, herpes zoster, multiple sclerosis, transverse myelitis, goiter, and iritis. In some cases the tendency of the streptococcus to localize electively was very striking, there being no lesions in other organs, while in other cases there were minor localizations in addition to specific localizations, indicating both a general and a specific virulence. In some the results were entirely negative. This was the case following injection of streptococci after aerobic plating on blood agar.

LOCALIZATION OF BACTERIA IN PUS EXPRESSED FROM TONSILS AND IN  
EMULSIONS OF EXTIRPATED TONSILS DIRECTLY INJECTED  
INTO ANIMALS

Some years ago, in studying the localizing power of the bacteria contained in tonsils in cases of rheumatic fever, "emulsions of freshly removed tonsils were found to be very toxic for rabbits, guinea-pigs, and dogs. Symptoms following injections of relatively large doses in guinea-pigs and dogs are those characteristic of anaphylaxis in each. The degree of toxicity was greatest in the emulsions from tonsils which were visibly infected and which showed the greatest numbers of bacteria in plate cultures."<sup>35</sup>

Dick and Burmeister made a more extensive study of the toxicity of extirpated tonsils; they also found that the toxicity is in proportion to the amount of evidence of infection, particularly by hemolytic

streptococci. These experiments indicate that ill effects must come from the continued absorption of toxic material from localized infections aside from the actual localization and growth of living bacteria in distant organs or tissues.

Those who are inclined to minimize the importance of foci of infection as causes of systemic disease have raised the objection that in animal experiments repeated large doses of cultures are given intravenously, and that therefore localization is to be expected, but that under natural conditions this does not occur. It is a fact that elective localizations have occurred in instances in which the dose of the culture injected was very small and they have occurred even following intraperitoneal injection. But in order to simulate the conditions more closely, direct injections of bacteria that had grown in the tonsils have been made in suitable cases together with cultures made from this material.

In Table 2 is given a summary of the results of these experiments. The figures indicate the percentage incidence of localization in the various organs as revealed to the naked eye at necropsy. The blank spaces indicate the absence of lesions in these organs. Most of the animals were injected intravenously directly with a small amount of material expressed from tonsils after it had been emulsified in salt solution. The rest were injected with small doses of emulsions from tonsils. The tendency to localize electively in the organs or tissues, corresponding to those involved in the patients from whom the material was obtained, was often a striking picture. This was particularly marked in cases of chronic arthritis and myositis when a number of experiments, sufficient to be of value, were made, although even when only a few animals were injected from cases of ulcer of the stomach, nephritis, neuritis, and erythema nodosum, localization occurred in the specific organ more often than in other tissues and the lesions were more distinct. The tonsils showing the largest amount of infected material are often small and atrophic. There is little evidence of inflammatory reaction. The infection is virtually outside the tonsil in walled-off pockets and hence localization in the tonsils of animals should not be expected after the intravenous injection. Besides, the tonsils of the animals used bear little resemblance to the human tonsil.

TABLE 2.—LOCALIZATION OF BACTERIA IN PUS EXPRESSED FROM TONSILS AND IN EMULSIONS OF EXTIRPATED TONSILS AFTER DIRECT INJECTION INTO ANIMALS

Diseases	Strains (44)	Animals injected (71)	Percentage of animals showing lesions in																								
			Tongue	Teeth	Skin	Thyroids	Muscles	Joints	Peritoneum	Intestines	Appendix	Stomach (hemorrhage)	Stomach (ulcer)	Duodenum (hemorrhage)	Gallbladder	Adrenals	Kidneys	Lungs	Pericardium	Myocardium	Endocardium	Nerves	Ganglia	Meninges	Spinal cord	Brain	
Chronic arthritis and myositis	24	37							3	5		10	3				15	15		10	15						
Ulcer of stomach	4	5			20		40					80	80	40							20						
Cholecystitis	1	2										50	50	50	50						100						
Nephritis	2	2										50						100									
Neuritis	4	8		13			25					13											50				
Herpes zoster	3	7	14		43		29	14																29			
Neuralgia	1	3						33			33																
Multiple sclerosis	4	6															66	66	33						33		
Erythema nodosum	1	1			100		100											17	17	34						17	17

The fact is now well known that acute exacerbations in symptoms follow the surgical removal of certain foci of infection in chronic diseases, especially those about the teeth. This is particularly likely to occur in persons with chronic disorders who appear to be hypersensitive. The danger from the removal of too many foci at one time, in these cases, was noted some years ago (1913) when a fatal exacerbation following the removal and curettement of a number of abscessed teeth occurred in a patient suffering from chronic arthritis. To quote:<sup>39</sup>

"On February 6, 1913, tonsillectomy was followed by slight increase in temperature for a day or two. On February 16, a number of teeth were extracted, followed on the next day by fever from 102° to 105°F. for nearly three weeks, associated with pericarditis, pleurisy with effusion, broncho-pneumonia, exacerbation of the joint sensitiveness, and successive crops of erythematous nodes of the skin chiefly over the forearms and legs, acute dilatation with acute multiple ulceration of the stomach shortly before death, February 28."

The sockets were curetted immediately after extraction. The importance of the gradual removal of foci, particularly in the dental area, in chronic diseases has since been emphasized especially by Hartzell,<sup>17</sup> by Thoma,<sup>49</sup> and by many others. The exacerbations may be due to the absorption of toxic material to which these patients are hypersensitive, to a lighting up of a more or less dormant infection in metastatic lesions, or to a localization of bacteria that gain entrance through the traumatized area from which the diseased tissue may have been only partly removed. That such localization occurs in some instances is indicated by the results obtained in the case quoted above, and by the fact that the bacteria contained in the material expressed from tonsils or contained in extirpated tonsils, in some persons who developed temporary exacerbations, showed elective localizing power in animals. Thus, a patient with simple thoracic herpes zoster developed a gangrenous herpes zoster following the expression of pus from the tonsils containing bacteria that produced herpes in animals.

#### ILLUSTRATIVE CASES AND EXPERIMENTS

Case 516.—A woman, aged 57, with typical transverse infectious myelitis, on examination showed marked pyorrhea. The patient had but seven teeth remaining, and these were loose in their sockets and surrounded by large amounts of pus. A moderate amount of pus was expressed from the tonsils.

Twenty-one animals were injected with the bacteria isolated from the pyorrheal pockets and tonsils of this patient. Fifty per cent of the animals developed lesions in the meninges and 66 per cent showed lesions in the spinal cord. Partial or complete paralysis which began in the hind extremities developed in many of the animals. Lesions in the cord consisted chiefly of hemorrhages in both the gray and white matter, and of leukocytic infiltration in the meninges and surrounding the blood-vessels. The results following the injection of cultures from the pus about the teeth were similar to those in the following experiment:

Rabbit 514 was injected intravenously, Oct. 31, 1915, with the growth from 60 c.c. of ascites-dextrose broth. November 1, peculiar incoördination was noted. The animal threw itself from side to side in attempting to get on its feet, which it was not able to do on account of weakness in the hind extremities. It was extremely ataxic, and was unable to maintain its equilibrium. The respirations were increased and it responded only slightly to a pin-prick in the hind extremities. November 2, the animal was found dead. Necropsy showed marked edema and hemorrhage of the pia. A blood-clot was found between the cerebrum and cerebellum. The external surface of the dura showed marked congestion and numerous hemorrhages. The spinal fluid was turbid and hemorrhagic. There were a few small hemorrhages in the gray matter of the cerebrum and a large number in the cerebellum. Cultures of the blood, spinal fluid, brain, and cord contained short-chained streptococci and a few colon bacilli. The meninges of the cervical cord showed marked leukocytic infiltration, especially around the nerve roots, but the nerve substance was free from infiltration. The infiltrating cells were chiefly polymorphonuclear leukocytes. The medulla showed marked hyperemia of the vessels but no hemorrhagic nor leukocytic infiltration of the dura. Gram-positive diplococci were found in and adjacent to lesions, but not in tissues free from lesions.

Case 595.—A middle-aged man had typical multiple neuritis which had followed an attack of so-called influenza three months before. (The details of the history of this case are reserved for a more complete report elsewhere.) The patient's tonsils appeared quite normal on the surface, but a moderate amount of pus was expressed from the poles of each. The teeth and gums were believed to be normal, and they appeared so on the surface, but on closer examination a marked pyorrhea was found about several of the molars.

Two series of nineteen animals were injected with cultures from tonsils and teeth, and lesions of the peripheral nerves occurred in 79 per cent. The results in animals injected with cultures from the pyorrheal pockets are illustrated in the following protocols:

Rabbit 739, weighing 2115 gm., was injected intravenously, March 13, 1916, with a growth from 7.5 c.c. of ascites fluid. March 14, the animal was found dead. At necropsy were found marked hemorrhagic infiltration of the right musculospiral nerve, acute splenitis, and several small areas of hemorrhage in the stomach. Numerous cross sections of brain and cord showed no lesions. The localization in the musculospiral nerve is illustrated in Figure 336A.



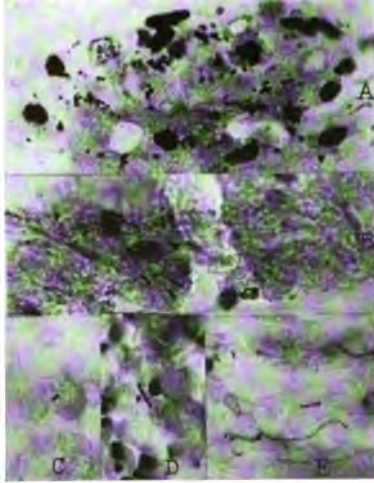


FIG. 336.

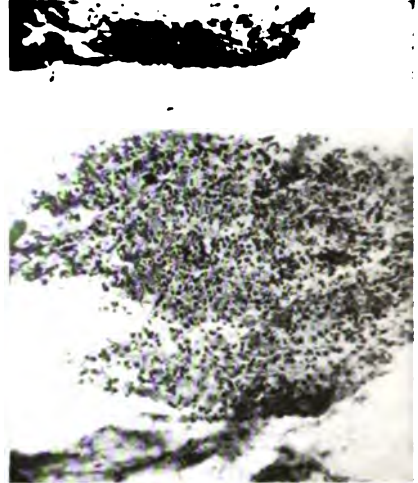


FIG. 337.

FIG. 336.—A. Diplococci and leukocytes in the right musculo-spiral nerve of Rabbit 739 injected intravenously with a culture from pyorrheal pockets in a case of multiple neuritis (Case 595).

B. Diplococci in the edematous area of the nerve shown in Figure 339.

C. Diplococci in the area of infiltration shown in Figure 337.

D and E. Chains of diplococci in the hemorrhagic and edematous areas in the nerve shown in Figure 338. Gram-Weigert,  $\times 1000$ .

FIG. 337.—Section of the left posterior tibial nerve of Rabbit 746 injected intravenously with the culture from pyorrheal pockets in a case of multiple neuritis (Case 595). Note the marked leukocytic infiltration and the separation of the nerve fibers. Hematoxylin and eosin,  $\times 200$ .

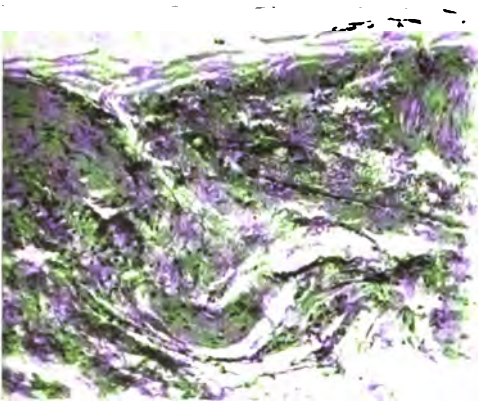


FIG. 338.

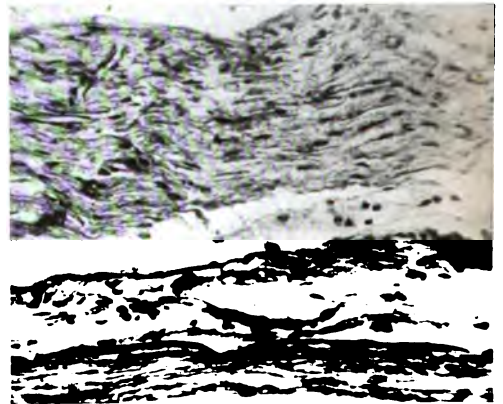


FIG. 339.

FIG. 338.—Section of anterior crural nerve of Guinea Pig 156 injected intraperitoneally with a culture from a pyorrheal pocket in a case of multiple neuritis (Case 595). Note the hemorrhage and leukocytic infiltration. Hematoxylin and eosin,  $\times 120$ .

FIG. 339.—Section of the left internal popliteal nerve of Guinea Pig 158 injected intravenously with a culture from pyorrheal pockets about teeth in a case of multiple neuritis after one animal passage. Note the edema, hemorrhage, and leukocytic infiltration, between the nerve fibers. Hematoxylin and eosin,  $\times 220$ .

Rabbit 746, weighing 1240 gm., was injected intravenously, March 17, 1916, with 10 c.c. of ascites fluid culture. March 19, the animal was found in a crouched position; it was disinclined to walk; it was lame in the left hind extremity which it held up as if it were painful. Its hair was fluffed. March 23, the symptoms were about the same. The animal was chloroformed, and at necropsy showed a large number of white lesions in the muscles, arthritis of both knees, hemorrhage, edema, and infiltration of both tibial nerves, most marked in the upper third of the left (Fig. 337), and localized infiltration and edema adjacent to and involving the small branches of the subcutaneous nerves in various parts of the body. Blood-agar plate cultures of the blood were sterile.

Guinea Pig 156, weighing 320 gm., was injected intraperitoneally, March 17, with 5 c.c. of ascites-fluid culture. March 18, the animal was found dead. Necropsy showed acute peritonitis and marked hemorrhage and edema of the lower end of both posterior tibial nerves. The lesions and localizations are illustrated in Figures 336, D and E, and 338.

Guinea Pig 158, weighing 330 gm., was injected intravenously, March 23, with 3 c.c. of ascites-dextrose-broth culture after the strain had passed through one animal. March 24, there were no symptoms. The animal was chloroformed, and at necropsy were found swelling and hemorrhagic infiltration in a localized area in the external and internal left popliteal nerves, in the lower third of the right sciatic nerve, in the right anterior crural nerves, in two of the trunks on both sides of the sacral plexus, and in the anterior trunk of the right brachial plexus. Cultures in ascites-dextrose on blood-agar plates of the blood, kidney, muscles, and cord, proved sterile. Cultures of the liver showed ten colonies of streptococci. Ascites-dextrose-agar shake cultures of the cord, kidney, and normal trunk of the sacral plexus remained sterile, while those of the liver showed two colonies, and those of the muscle one colony, of streptococci. The type of lesions in the nerves and the localization of the bacteria are illustrated in Figures 336B and 339.

Case 621.—A woman, aged 53, with chronic multiple arthritis and myositis, soon after a pregnancy, twenty years before examination, began to have pain in the right shin just below the knee. This was temporarily relieved by hot baths, but later pain and stiffness developed in the knee, and with it pains passing from joint to joint. A vaccine prepared from *Streptococcus rheumaticus* was used and potassium iodid was administered, resulting in great improvement which lasted for two years. The patient then developed pain in the jaws and teeth, and the joint symptoms returned. An x-ray examination disclosed abscessed teeth, which were removed. The tonsils had been removed seven months before with some improvement. A general examination revealed multiple arthritis in all the large joints with marked destruction of joint surfaces, as shown by the x-ray, ankylosis of the knees, and almost complete fixation of both elbows. A small amount of infected lymphoid tissue in the region of the tonsil scars was found and removed. X-ray examination revealed rarefaction around the apices and roots of the first left upper molar. This tooth was extracted. Small masses of connective tissue over the

apices of the roots and a partially calcified pulp were found. Improvement in the patient's condition following the removal of these foci was slight and temporary; this could be expected considering the marked changes that had already occurred.

Cultures from the granuloma of the extracted tooth in dextrose broth yielded a large number of green-producing streptococci and a few hemolytic streptococci, while those made from the pulp contained pure cultures of green-producing streptococci. Those from the tonsils showed green-producing streptococci, *Micrococcus cattarhalis*, staphylococci, and small Gram-positive bacilli.

The primary cultures in dextrose broth of each were injected into four animals. Non-suppurative arthritis, lesions in the ligaments and the periosteum around joints and muscles, chiefly in the tendinous portion, were the predominating findings in all the animals. The two injected with the culture from the pulp also showed lesions in the pulps of teeth, while the two injected with the culture from the granuloma and tonsil, respectively, did not.

Rabbit 813, weighing 1750 gm., was injected intravenously, April 27, 1916, with 10 c.c. of ascites-dextrose-broth culture from the apex of the extracted tooth. April 28, when the animal seemed quite well, it was chloroformed. Examination revealed a large hemorrhage in the periosteum on the inner aspect of the tuberosity of the left tibia, slightly turbid fluid in both knee-joints, a number of hemorrhages in the muscles and tendons about the hip-joints, a moderate number of small whitish streaks in the flat muscles about the chest and diaphragm, and over the tendinous portions of the muscles of the extremities. There were two hemorrhages in the tricuspid valve, two small ones along the lesser curvature of the stomach, and a large hemorrhagic ulcer near the pylorus. There were no other lesions. Blood-agar-plate cultures from the blood and joint fluid were sterile, while cultures in ascites-dextrose-broth showed green-producing streptococci.

Rabbit 814, weighing 1210 gm., was injected intravenously, April 27, 1916, with 10 c.c. of ascites-dextrose-broth culture from the pulp of the extracted left upper molar. April 28, the rabbit seemed quite well; it was chloroformed. At necropsy there were found distinctly turbid fluid in both knee-joints; a few hemorrhages in the capsule and muscles around the left knee-joint and left shoulder-joint; a few lesions in the muscles, especially in the tendinous portions about the extremities; and hyperemia and hemorrhages in pulps of teeth.

Rabbit 820, weighing 1240 gm., was injected intravenously, April 28, 1916, with the growth from 30 c.c. of ascites-dextrose-broth culture from the pulp of the extracted tooth. April 29, the rabbit seemed in pain and its muscles were sore. It was chloroformed and at necropsy showed a number of hemorrhages in the periosteum near the tuberosity of the tibia, and marked hyperemia and small hemorrhages of the pulps of the teeth.

Rabbit 823, weighing 1420 gm., was injected intravenously, April 29, 1916, with 10 c.c. of ascites-dextrose-broth culture from the tonsil. May 1, the rabbit seemed quite well but was distinctly muscle-sore. The animal was chloroformed. A small number of lesions was found in the muscles about the knee- and hip-joints, especially in the tendinous portions; also arthritis of the left knee, hemorrhages in the periosteum of the lateral aspect of the tibia, and hemorrhages in the periosteum under the left eye.

Case 623.—G. W., a middle-aged physician, had repeated attacks of pain in the right gluteus maximus muscle, and occasional stiffness of the muscles of the back. The attacks varied from time to time and were much less severe after the removal of the tonsils at the end of three years, but they recurred at intervals and the patient was not quite free from stiffness and soreness in the interim. On examination at the Mayo Clinic, in April, 1916, a small abscess was found over the apex of a tooth, which was extracted. A small granuloma was found over the apex of the root of the extracted tooth and the canal showed a calcifying pulp. Slow but continuous improvement followed, with entire freedom from severe attacks for several years, even during ten months in the damp, cold climate of France.

Cultures from the granuloma and pulp showed short-chained, green-producing streptococci, a few staphylococci, a few hemolytic streptococci, and a moderate number of slightly hemolyzing streptococci.

A primary culture of the calcified pulp was injected into one rabbit, the primary culture of the granuloma into another. The results obtained from the injections are recorded:

Rabbit 818 was injected intravenously, April 28, 1916, with the growth from 30 c.c. of ascites-dextrose broth from the granuloma. April 29, the animal seemed muscle-sore but otherwise well. It was chloroformed and at necropsy the fluid in knee-joints and shoulder-joints was found distinctly turbid. The right gluteus muscle was streaked with white and was hemorrhagic; and an area, almost 1 cm. in diameter, near the attachment of the muscle to the ilium, contained numerous small hemorrhages. A moderate number of lesions were scattered in the more tendinous portions of the muscles throughout the body and in the muscles about the shoulder blades. Cultures from the blood and joint fluid showed a pure culture of green-producing streptococci; those from the muscle showed a large number of slightly hemolyzing streptococci, a few green-producing streptococci, and a few Gram-negative bacilli. The microscopic appearance of the lesions in the gluteus maximus muscle and the localization are illustrated in Figures 340 and 341D.

Rabbit 822, weighing 1220 gm., was injected intravenously, April 29, 1916, with 10 c.c. of ascites-dextrose-broth culture from the partially calcified pulp of the extracted tooth. At 3.00 p.m. the rabbit was found dead. Examination revealed numerous small hemorrhages, over an area 1 cm. in diameter, in the right gluteus maximus muscle near its attachment to the ilium. A group of hemorrhages in the other muscles about the right hip-joint and a few lesions in the muscles on the right side of the chest were found. Cultures of the blood were sterile.

Case 628.—A woman, aged 54, had suffered from severe shooting pain in the lumbar region and back, and down the right leg to the inner side of the knee, for a period of three or four weeks fifteen months before. She had had an acute attack of cystitis eighteen months

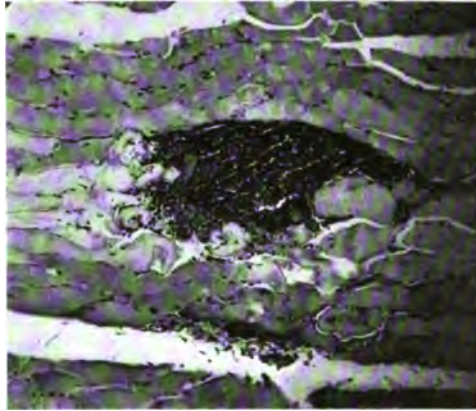


FIG. 340.—Lesion in the gluteus maximus of Rabbit 818 injected with a culture from a granuloma in a case of recurring attacks of gluteus myositis (Case 623). Note the sharply circumscribed leukocytic infiltration and destruction of the muscle fibers. Hematoxylin and eosin,  $\times 100$ .

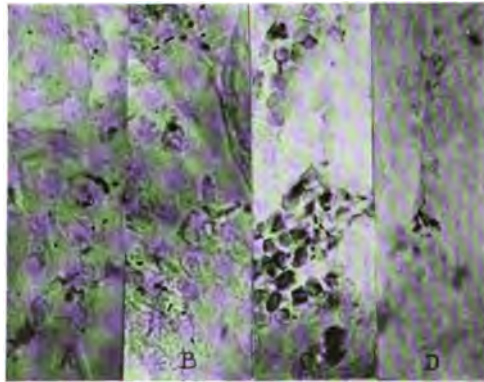


FIG. 341.—A, Section of hemorrhagic and edematous peridental membrane of a tooth of a guinea pig injected intravenously with a culture of streptococcus from foul dental pulp in a case of pulpitis, dental neuritis, and myositis. Note the large number of diplococci. Gram-Weigert,  $\times 1000$ .

B, Diplococci in the vagus ganglion in a rabbit injected intravenously with a culture of streptococcus from a case of pulpitis, dental neuritis, and myositis associated with marked vagotonic neurosis.

C, Diplococci in the hemorrhagic area of the sympathetic ganglion in the same rabbit (B).

D, Diplococci in the area of infiltration in the muscle shown in Figure 340. Gram-Weigert,  $\times 1000$ .

before, at which time the course of the nerve on the inner aspect of the leg was eruptive and blistered. Five months before coming to the clinic the patient had an attack, less severe, lasting three or four weeks; and, during the previous winter, weakness in the back and numbness in both thighs had been noted. X-ray examination of the lumbar spine was negative; the joints showed ankylosis. Abscesses were found at the roots of the lower right third molar and second bicuspid. The tonsils, which showed moderate infection, were removed. The teeth were extracted. The root canals were almost obliterated; neither of them was foul.

Cultures from the tonsils showed hemolytic and green-producing streptococci; and cultures from the small abscess at the apex of the molar showed a pure culture of green-producing streptococci in pairs, and in long and short chains.

Cultures from the tonsils, from the small granuloma at the apex of the molar, and from the pulp of the bicuspid, were injected into animals. The following protocols illustrate the marked tendency to localize in the lumbar nerves, and dorsal roots and ganglia:

Rabbit 839 was injected intravenously, May 20, 1916, with 10 c.c. of ascites-dextrose-broth culture from the granuloma at the apex of the molar. May 21, the animal was found dead. Necropsy showed a number of punctate hemorrhages in the nerve substance of the left external popliteal nerve and its branches to the calf of the leg. The nerve sheath was hyperemic and also showed hemorrhages. In the left sciatic nerve was one small punctate hemorrhage, in the right sciatic nerve a few hemorrhages, and one small hemorrhage was found in the right posterior tibial nerve. Very small punctate hemorrhages dotted the skeletal muscles. The external dural venous plexus was hyperemic. The spinal roots and the membranes of the cord were free from hemorrhages, except for a sharply circumscribed subpial hemorrhage, 3 by 4 mm., surrounding the right second sacral anterior root, and one smaller hemorrhage surrounding the nerve just beyond the ganglion of the third sacral root. Numerous cross sections of the cord showed no lesions in its substance. Cultures from the blood showed pure culture of short-chained streptococci.

Rabbit 842 was injected intravenously, May 22, 1916, with 10 c.c. of ascites-dextrose-broth culture from the pulp of the lower right third molar. May 23, the animal seemed well; the injection was repeated. May 25, it seemed well and was chloroformed. Necropsy revealed a few lesions of the muscles over the left hip and psoas. Distinct hemorrhagic edema surrounded the posterior roots of the fourth left cervical, and third and fourth left dorsal ganglia; and the extradural vessels in the lumbar region were markedly congested. Numerous cross sections of the brain and cord showed no lesions. Cultures of the blood in ascites-dextrose broth showed a pure growth of streptococci.

Rabbit 845 was injected intravenously, May 24, 1916, with 5 c.c. of ascites-dextrose-broth culture of the streptococcus isolated from the rabbit injected with the primary culture from the tonsil. May 26, the animal moved about as if in pain; it was chloroformed. Necropsy revealed a few small hemorrhages in the bladder, a few white embolic foci in the cortex of the kidney, localized myocarditis, arthritis of both knee-

joints, a few lesions in the muscles, and localized areas of hemorrhage and edema of the sheaths of the main trunks of the lumbar plexus (Fig. 342). There was one area of hemorrhage and infiltration in the right external popliteal nerve, and also hemorrhagic edema of the external surface of the dura posteriorly and surrounding the posterior dorsal roots, chiefly in the cervical region.



FIG. 342.—Nerve trunks of the lumbar plexus and sciatic nerve in Rabbit 845 injected with a culture from the tooth in the case of lumbar neuritis (Case 628). Note the hemorrhagic areas in the former and the absence of lesions in the latter,  $\times 2$ .

**Case 630.**—A druggist, aged 46, had had two attacks of epilepsy in the six weeks before his examination, and red spots had appeared on the forehead and to the right of the midline, extending back over one-half of the right side of the head. One week later, he began to suffer severe pain in the region of the right eye. A typical herpes zoster was found over the right side of the face and forehead. The tonsils were moderately infected, and x-ray examination of the teeth revealed an abscess at the roots of the lower left molar. The tonsils were removed, and the tooth was extracted.

A series of five rabbits was injected with cultures from both. Four rabbits were injected with cultures from the tonsils before and after one animal passage; all showed herpes. The result in the rabbit injected with the culture from the granuloma at the apex of the tooth is indicated in the following protocol:

Rabbit 848, weighing 1160 gm. was injected intravenously, May 23, 1916, with 10 c.c. of ascites-dextrose-broth culture. May 26, the animal sat around as if in pain; it was chloroformed. Necropsy showed numerous small vesicles with opaque bases on the dorsum of the tongue, chiefly on the left side. The vesicles were not ruptured and were from 0.5 to 2 mm. in diameter. The right gasserian ganglion showed a number of subcapsular hemorrhages, and a few hemorrhages were found in the valves of the heart. No lesions were found in numerous cross sections of the brain and cord. Cultures from the blood in ascites-dextrose broth showed streptococci.

Case 674.—A man, aged 53, had suffered from typical bilateral trigeminal neuralgia for twenty years. (The details of the history are reserved for a more complete report elsewhere.) The patient's tonsils were of moderate size, red, and contained a small amount of pus. Many of his teeth had been extracted, and the gums were retracted from those remaining. Pyorrhea was marked.

Cultures from the pus expressed from the teeth and tonsils were injected into animals. The results are illustrated in the following protocol:

Rabbit 908 was injected intravenously, July 12, 1916, with the growth from 30 c.c. of ascites-dextrose-broth culture from pus from around the teeth. July 14, the animal was found dead. Necropsy revealed a large hemorrhagic edematous area surrounding the right inferior dental nerve at the point of exit; a few distinct hemorrhages in the nerve sheath; a large hemorrhage and marked edema of the right superior dental nerve, extending for a distance of 1 cm. in the bony canal; multiple hemorrhages and hyperemia of the left inferior dental nerve within the submaxillary bone; and marked hyperemia, but no gross hemorrhages, in the pulp of the teeth in the left lower jaw. The injected culture contained streptococci and a Gram-negative bacillus. Blood-agar-plate cultures of the blood after death showed a few streptococci and a moderate number of Gram-negative bacilli. Microscopic sections were made of the sensory root of the right gasserian ganglion, of the left inferior dental nerve, of the tooth pulp, of both superior maxillary nerves, and of the gasserian ganglia. The lesions and localizations found in these areas are shown in Figures 343 and 344 A and B.

Case 3368.—A man, aged 47, wood-worker by occupation, complained of feeling below par generally, and of recurring mild attacks of rheumatic pains in the back, arms, shoulders, and through the head. The attacks tended to recur at intervals of about one month for the past three or four years. The patient also complained of a burning sensation in the mouth. A general examination was negative; systolic blood pressure, 136; diastolic pressure, 66; Wassermann test, negative. An x-ray examination of the head showed cloudy maxillary sinuses, and apical rarefaction about three teeth. The first right upper bicuspid gave no evidence of rarefaction over the apex, but was somewhat discolored, and an electric test indicated lost vitality of the nerve. The four teeth were extracted, and the



bicuspid was sent for cultures by Dr. Gardner. No evidence of infection over the apex was found. The surface of the tooth was sterilized in a Bunsen flame, wrapped in sterile gauze and split open in the

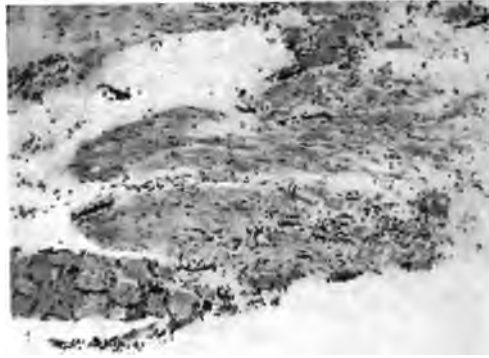


FIG. 343.—Section of gasserian ganglion in Rabbit 908 injected with a culture from pus about teeth in a case of trigeminal neuralgia (Case 674). Note the hemorrhage and leukocytic infiltration. Hematoxylin and eosin,  $\times 100$ .

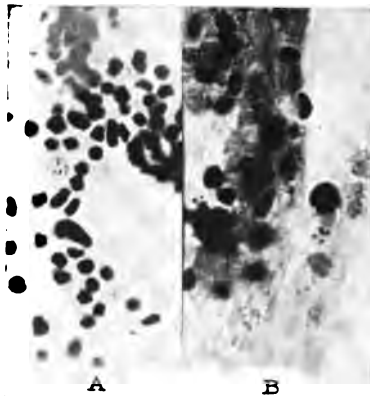


FIG. 344.—A. Small diplococci in the hemorrhagic and edematous area of the gasserian ganglion in rabbit injected intravenously with the dextrose-brain-broth culture of streptococci isolated from the tissues about the apex of a second lower bicuspid devitalized twenty years before.

B. Small diplococci in the sensory root of the gasserian ganglion in the same animal. Gram-Weigert,  $\times 1000$ .

jaws of a vise. The pulp appeared quite normal, although it was slightly hyperemic, particularly over a small lateral area.

After the surface of a blood-agar plate had been inoculated, the

pulp was placed in the bottom of a tall tube of dextrose-acacia broth, and incubated for ten hours. It was then placed in 10 per cent formalin. A pure culture of a short-chained streptococcus developed in the broth; it showed preference for anaerobic conditions, growing only in the lower two-fifths of the column of the broth (Fig. 326, Tube I). Microscopic examination of stained sections of the pulp showed practically no abnormalities except a small area of round-cell infiltration along one margin (Fig. 332). Sections of the pulp, after incubation in the broth for ten hours, showed a number of capillaries plugged with streptococci (Fig. 332), together with large numbers of bacteria in the area of infiltration (Fig. 333).

The primary broth culture was injected intravenously into two rabbits. The one developed marked double iritis, hemorrhage and infiltration in the pulps of teeth, and a number of hemorrhages in the muscles. The rabbit which received a smaller dose showed symptoms of iritis, injection of vessels, photophobia, and lacrimation for a number of days, and then recovered. The animal was anesthetized on the third day. Slightly turbid fluid in the knee-joints was found, but no other lesions.

Cultures from the iris of the rabbit that showed marked iritis (Fig. 326, Tube III) were injected into two rabbits. Both of these developed temporary symptoms of iritis. One had outspoken lesions of the pulps of the teeth, and both had lesions in muscles and joints. One also had hemorrhage in the stomach and heart valves. The following experiments illustrate the results obtained with the culture from the focus in this case:

Rabbit 1720, weighing 1610 gm., was injected, April 15, 1919, with 7 c.c. of a forty-eight hour dextrose-acacia-broth culture from the pulp of the right upper first bicuspid. April 16, the left eyelids were glued together by exudate. The vessels of the iris and of the sclera surrounding the cornea were markedly congested, but there was no turbidity of the anterior chamber. The right eye was normal. The rabbit appeared muscle-sore, generally weak, and its respirations were slightly increased. April 17, there was marked injection of the vessels of the iris and sclera surrounding the cornea in both eyes. The right eye was enucleated by Dr. Benedict. Examination showed hemorrhagic exudate in the posterior surface and peripheral margins of the iris (Fig. 345). The rabbit appeared to be weak and muscle-sore, and tended constantly to crouch and to lie on its side as if it were painful to stand. April 18, the animal was extremely weak, and just able to walk. The fluid in the anterior chamber of the left eye was very turbid. The rabbit died at 10.30 a.m. Examination showed a moderate number of hemorrhagic lesions of the muscles, especially surrounding the nerve trunks of the abdominal wall; also small hemorrhages of the tendinous portion of the muscles of the extremities and deep muscles of the shoulder and hip joints. The periodental membrane on the left lower incisor, especially near the apex, and the pulp of the tooth were hemorrhagic and edematous (Fig. 346), and microscopically the pulp showed leukocytic infiltration and diplococci adjacent to or in hemorrhagic areas (Fig. 347). In the corresponding left inferior dental nerve was a number of small punctate hemorrhages. The pulp of a number of the molars was hemorrhagic. A few small circumscribed hemorrhages were found in the cecum. The uterus contained three necrotic placental masses; the peritoneum over these areas was hyperemic and covered with a



FIG. 345.—Section of the ciliary body and iris of Rabbit 1720, injected with the culture from the dental pulp in Case 3368, showing marked hemorrhage and infiltration. Methylene blue and eosin,  $\times 50$ .

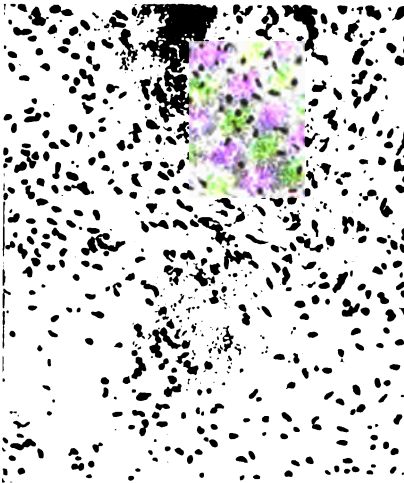


FIG. 346.



FIG. 347.

FIG. 346.—Section of the pulp of the left lower incisor of Rabbit 1720 injected with the culture from the pulp of the tooth in Case 3368. Note the areas of hemorrhage and leukocytic infiltration. Hematoxylin and eosin,  $\times 200$ .

FIG. 347.—Section of the dental pulp illustrated in Figure 346 showing diplococci, leukocytes, and hemorrhage adjacent to the capillary. Gram-Weigert,  $\times 1000$ .

thin layer of fibrin. The lungs, stomach, heart, kidneys, adrenals, superior dental nerves, joints, brain, and cord were free from lesions. Blood-agar plates and tall-tube cultures in dextrose-broth of the vitreous and turbid fluid in the anterior chamber of the extirpated eye were negative. Blood-agar-plate cultures of the turbid fluid of the anterior chamber of the left eye after death showed a moderate number of green colonies of streptococci and a few colonies of colon bacilli. Dextrose-acacia-broth cultures of this fluid contained many colonies in the fibrinous film in the middle portion of a tall tube, but no diffuse growth. A diffuse cloud in the lower 2 cm., but no growth in the rest of the tube, developed in the dextrose-acacia-broth cultures from the iris of the extirpated right eye (Fig. 326, Tube II). Cultures from the iris of the left eye, after death, in dextrose-blood broth, showed a marked diffuse cloud in the lower half of the tube, and a less dense cloud in the upper half, due to the short-chained streptococci in pure culture. A few colonies of green-producing streptococci developed in blood-agar-plate cultures from the fresh hemorrhagic pulp of the left lower incisor, while those from corresponding normal pulp of the right upper incisor were sterile. A moderate number of green-producing streptococci and a few colon bacilli were found in cultures from the blood.

Case 3458.—A woman, aged 23, came to the clinic because of pain in the left eye. Three days before a foreign body had become lodged in her eye, causing considerable pain and lacrimation. The eye was washed with boric acid solution, and the patient felt relieved, though the pain prevented her from sleeping during the night. The following day, while she was working, the eye gradually became more painful. Dr. Benedict found injection of the conjunctiva, a clear cornea, a normal fundus, but no evidence of a foreign body. The patient subsequently developed a typical attack of keratitis and iritis (Plate II(1)). A general examination was negative. The dental examination by Dr. Gardner showed four impacted molars, and a fracture of the roots of both upper central incisors, sustained eleven years previously. The impacted and fractured teeth were extracted, and the sockets of the incisors curetted. The patient made a rapid recovery. The pulp of the right upper central incisor was calcified; the pulp chamber of the left upper central incisor was enlarged and filled with foul-smelling pus, and this tooth had a small granuloma over its apex.

Gram-positive diplococci were identified in smears from the pus; also a large number of fusiform bacilli, and cocci of varying sizes. A blood-agar plate of this pus produced a moderate number of indifferent colonies of staphylococci, but no green nor hemolytic streptococci. Cultures in dextrose-blood broth of the foul pulp produced a diffuse cloud, due to short-chained streptococci. A blood-agar plate of this culture showed green-producing streptococci in pure form. Cultures in dextrose-blood broth of the granuloma over this tooth, of a

splinter of bone from between the two teeth, and of the calcified pulp of the right incisor, showed in twenty-four hours a diffuse cloud in the lower two-thirds of the tube, gradually rising to the top. The same type of streptococcus was isolated from blood-agar plates of the dextrose-blood-broth culture as from the foul pulp. Microscopic sections of the granuloma showed chiefly old dense fibrous tissue containing various sized, highly cellular areas (Fig. 348). The areas of infiltration contained fibroblasts, plasma cells, endothelial cells,

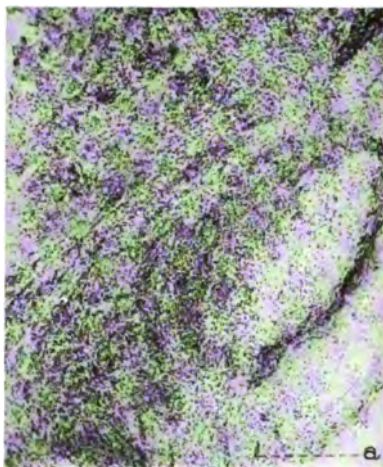


FIG. 348.

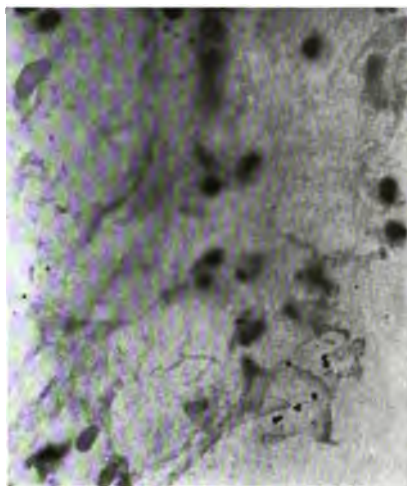


FIG. 349.

FIG. 348.—Granuloma at the apex of the left upper incisor of Case 3458. Note the irregular large and small areas of cellular infiltration, and the embryonic and sclerotic connective tissue. Hematoxylin and eosin,  $\times 50$ .

FIG. 349.—Granuloma shown in Figure 348. Gram-positive diplococci at a, in Figure 348. Gram-Weigert,  $\times 1000$ .

arranged in rows resembling capillaries, and a moderate number of leukocytes. Gram stain of the fresh granuloma showed an occasional diplococcus, usually in or adjacent to the cellular areas or blood vessels. At the apex of the granuloma near a blood vessel was found an area (Fig. 348) which contained a considerable number of diplococci (Fig. 349).

Primary dextrose-blood-broth cultures of the foul pulp, of the calcified pulp, and of the granuloma were injected intravenously into three rabbits, respectively. All of these had iritis and lesions of nerve trunks, and one had lesions of the muscles. The first two (Rabbits 1699, 1700) had marked lesions of the pulps and contiguous structures of teeth, the third did not. The culture of streptococcus from the iris of one rabbit

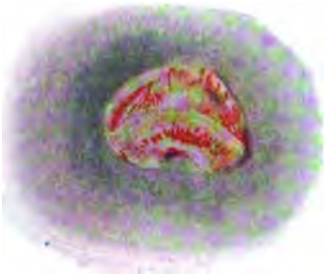
PLATE II



1



2



3



4

1. Drawing illustrating the condition of the eye in a case of keratitis and iritis with dental sepsis (case 3458). 2. Iritis in rabbit 1699 following injection of a culture from the foul pulp in a case of keratitis and iritis (case 3458). 3. Reverse side of the iris shown in figure 2. 4. Normal iris of an albino rabbit.



(Rabbit 1699) was injected into two others. Both developed lesions of the muscles, and lesions around the pulps of teeth and dental nerves and in the jaws. Only one of the five rabbits died from injections; the others were anesthetized for examination in from three to six days.

Rabbit 1699, albino, weighing 1100 gm., was injected intravenously. April 30, 9.00 a.m., with 3.5 c.c. of the dextrose-blood-broth culture of the foul pulp. A small amount of sterile sand was added to a few drops of this culture and placed in the right conjunctival sac. At 8.00 p.m. the vessels of the iris and surrounding conjunctiva were congested, and both eyes were affected by lacrimation and photophobia. The rabbit seemed well otherwise. May 1, 7.00 a.m., the congestion of the vessels of the eyes was more marked (Plate II(2)) and the animal appeared muscle-sore, inactive, with a tendency to crouch on its abdomen. The fluid in the anterior chambers was

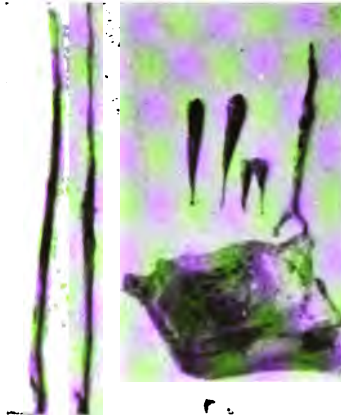


FIG. 350.—Photograph of hemorrhagic dental pulps, left inferior dental nerve, posterior tibial nerves, and superficial muscles and aponeurosis of Rabbit 1699 injected intravenously with a culture from the foul pulp of the left upper central incisor in Case 3458.

cloudy. At noon, the animal appeared weaker; congestion in the eyes had diminished. At 8.00 p.m., the animal jumped out of its basket in a convulsive seizure and died in violent convulsion fifteen minutes later. The circumcorneal congestion disappeared as death occurred.

The examination was made immediately. The iris of each eye was opaque and showed focal hemorrhages. The fluid in the anterior chamber was turbid. There were numerous hemorrhages of the posterior aspect of the iris and in the ciliary body (Plate II(2)). The base of the appendix and the mesenteric lymph glands draining the appendix were swollen and hemorrhagic. There was marked degeneration of the myocardium, hemorrhages of the superficial muscles and aponeurosis about the thorax (Fig. 350), punctate hemorrhages in the thymus, numerous subendothelial hemorrhages in the septal wall, in the left ventricle, and in the pupillary muscles. The parathyroid glands were extremely red and appeared edematous and swollen. The thyroid was hyperemic. In the first centimeter of the duodenum were a few small punctate hemorrhages; the mucous membrane of the cardiac end of the stomach was hyperemic; the lymph glands beneath the angle of the jaw and ear, and along both superior maxillary nerves, were



edematous and hemorrhagic; the axillary and inguinal lymph glands were normal; those in the popliteal spaces were hemorrhagic and edematous, and the posterior tibial nerves were swollen and hemorrhagic. The periosteum (Fig. 350) opposite the right lower incisor was edematous and easily separated from the bone; the tooth was loose in the socket; the periodontal membrane and the pulp were edematous and hemorrhagic.

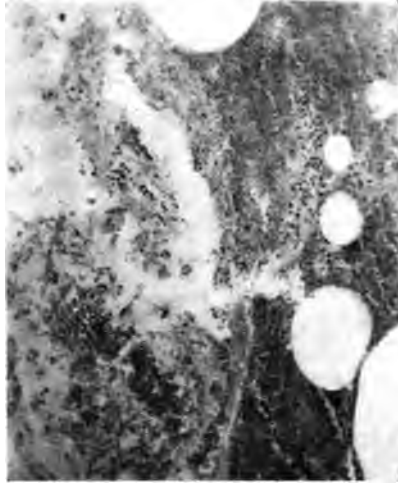


FIG. 351.—Section of the uvea of the eye of Rabbit 1699, shown in Plate II, (2) injected with a culture from the tooth in the case of keratitis and iritis. Note the marked hemorrhagic and leukocytic infiltration. Hematoxylin and eosin,  $\times 100$ .

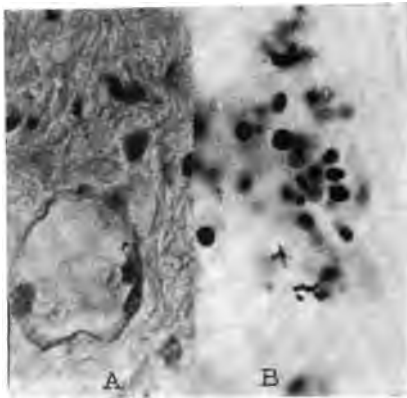


FIG. 352.—A. Diplococcus in capillary of hemorrhage ciliary body shown in Figure 345. B. Diplococci in the hemorrhagic area shown in Figure 351. Gram-Weigert.  $\times 1000$ .

The corresponding inferior dental nerve was hemorrhagic and a number of the pulps of the molars on that side were hemorrhagic and edematous (Fig. 350). The pulp of the left lower incisor, and the left inferior dental nerve, were normal. The superior dental nerves were edematous and contained a few punctate hemorrhages. Smears

from the hemorrhagic area in the periosteum and from three dental pulps showed a Gram-positive diplococcus, but no other bacteria. Blood-agar-plate cultures of the blood, of the fluid from the anterior chamber, and of the pulp of the right lower incisor, were negative. Dextrose-blood-broth cultures of the tissue of the iris, and the pulp of the right lower incisor, showed diffuse growth of a short-chained streptococcus, beginning at the bottom of the tube and gradually forcing its way to the top. Sections of the eyes showed marked hemorrhage and leukocytic infiltration of the ciliary body and iris (Fig. 351). Gram stains showed scattered diplococci in and adjacent to areas of hemorrhage (Fig. 352, B).

Rabbit 1700, a female weighing 1720 gm., was injected intravenously, April 30, with 5 c.c. of the dextrose-blood-broth culture from the calcified pulp of the right upper central incisor. A few drops of culture were mixed with sterile sand and dropped into



FIG. 353.—Posterior tibial and accompanying nerves and fascia of Rabbit 1700 injected with cultures from the calcified pulp in Case 3458. Note the extreme swelling and hemorrhage of the nerve and surrounding structures of the right leg including the bursa at the attachment of the tendon Achilles as compared with the same structures in the opposite side.  $\times 1$ .

the right conjunctival sac. May 1, the animal appeared fairly well, but there was lachrimation and moderate congestion of the vessels of both eyes. May 2, the eyes appeared normal, and the rabbit seemed well generally. The animal did not use the right hind leg, which it held up as if it were painful. Slight pressure along the sciatic nerve and posterior aspect of the legs seemed to cause pain. The joints were not swollen. May 3, conditions were about the same, and chloroform was administered slowly; the animal went to sleep without a struggle.

Marked infiltration and edema of the subcutaneous tissue of the posterior and lateral aspects of the lower two-thirds of the right leg and plantar surface of the foot were found. There was hemorrhage and infiltration along the sheaths of the nerve trunks and sheaths of the plantar surface of the right foot. This infiltration was most marked immediately surrounding the lower one-third of the posterior tibial and accompanying

nerve in the right leg. The tissues surrounding these nerves were extremely edematous and swollen, including the tendon Achilles and its bursa on the posterior aspect of the os calcis (Fig. 353). The plantar infiltration and suppuration followed the nerve trunk and extended into the tissues and sheaths of the tendons. The ankle and phalangeal joints were normal. The left posterior tibial nerve showed a few hemorrhages in the upper one-third, and the bursa of the attachment of the tendon Achilles was only slightly swollen. A number of small hemorrhages was associated with whitish streaks

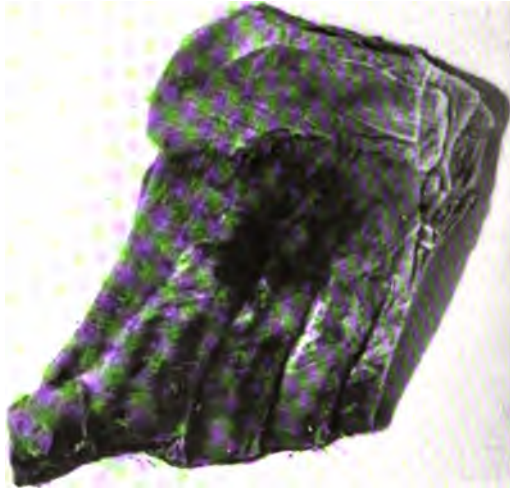


FIG. 354.—Hemorrhagic area of intercostal muscles of Rabbit 1700.

and localized edema in the more tendinous portion of the muscles of the anterior aspect of the left tibia, with a large area surrounding a small nerve in the deeper layer of the muscles. There was an area of hemorrhage and infiltration in the intercostal muscles beneath the shoulder blade of the right thorax (Fig. 354), and a large hemorrhage associated with edema in the periosteum of the upper left jaw opposite the apex of the upper left incisor (Fig. 355). The left superior dental nerve was hemorrhagic and edematous, with a number of whitish areas of infiltration. The pulp of the left upper incisor was hyperemic and edematous. The pulps of the molars on the left side were edematous; those on the right side appeared normal. The right superior dental pulp and nerve were normal. There were no lesions of the nerve trunks other than those mentioned.

The uterus was much enlarged and contained five almost full-term fetuses. In the first fetus were a few whitish lesions of the muscles of the abdominal wall along the blood vessels and nerve trunks; a few hemorrhages in the muscles about the neck and between the toes in the subcutaneous tissues of the plantar surface of the left foot;

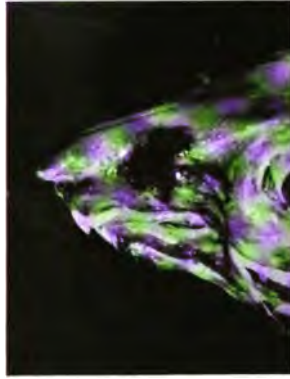


FIG. 355.—Hemorrhagic and edematous area in the upper jaw of Rabbit 1700.



FIG. 356.—Hemorrhagic area of intercostal muscles of Fetus 4, Rabbit 1700.

hemorrhage and edema in the posterior aspect of the left leg; and around the ankle joint of the right leg was a group of hemorrhages. In the second fetus was a group of hemorrhages between the third and fourth toes and in the upper aspect of the little toe, and a group of hemorrhages in the muscles of the anterior aspect of the left ear. In the

third fetus was a number of hemorrhages of the muscles of the inner and upper aspects of the left tibia. In the fourth fetus the only lesions were small punctate hemorrhages of the intercostal muscles and muscles of the back (Fig. 356). In the fifth fetus were small hemorrhages in the skin over the left shoulder blade.

Cultures from the heart blood and amniotic fluid of the adult rabbit were negative. Cultures from the pus around the right posterior tibial nerve of the adult rabbit showed countless numbers of colonies of green-producing streptococci. In the smears were moderate numbers of diplococci. No growths were produced from cultures of the fluid in the eyes and brain substance of two of the fetuses, while dextrose-blood broth inoculated with the hemorrhagic muscles of the left leg of the third fetus showed, in twenty-four hours, diffuse growth of short-chained streptococci in the lower portion of the tube, that rose to the top in seventy-two hours. In the blood-agar plate of this culture was the type of green-producing streptococcus injected into the adult rabbit in pure form.

## SUMMARY AND DISCUSSION

### EXPERIMENTAL FINDINGS

By the use of the method described it is possible to obtain fairly accurate information of the number and kind of microorganisms in various dental infections, as well as their location in relation to the blood supply. The cultures from apical abscesses and pulps of teeth, in my hands as in the studies of Hartzell and Henrici, Moody, and others, showed the green-producing streptococcus, often in predominating numbers, as an almost constant organism in these areas. A detailed study of some of the isolated strains is reserved for a more extensive study of streptococci from various sources. Streptococci were often isolated in pure culture, in some instances even though smears from the foul-smelling pus also showed staphylococci and fusiform bacilli. All the cultures of streptococci manifesting a preference for anaerobic conditions in the primary culture, as illustrated in Figure 1, ultimately became aerobic when, with few exceptions, they resembled *Streptococcus viridans*. In no instance did they remain strictly anaerobic. Slightly hemolyzing and indifferent streptococci and indifferent staphylococci occurred next in frequency. The fusiform bacillus was found almost constantly in pulp chambers or abscesses containing foul-smelling pus, but never in pure culture. Colon bacilli were commonly found, together with streptococci, staphylococci, fusiform bacilli, and spirochetes, in pyorrhea pockets, but they were only rarely isolated from apical infections.

The percentages indicating the localizations in the experiments summarized in Tables 1 and 2 do not adequately represent the results

obtained. In the former, injections were frequently made after plating the organisms, and, in both, lesions in organs, other than those affected in the patient harboring the focus, were usually less marked or trivial. The experiments in animals, recorded in detail, revealed the striking tendency of the bacteria to localize in the tissues involved in each of the following diseases: transverse myelitis, multiple neuritis, chronic arthritis and myositis, gluteus myositis, lumbar neuritis, herpes zoster, trigeminal neuralgia, mild myositis, keratitis, and iritis.

The results following injection of bacteria contained in small amounts of pus from tonsils show that the bacteria grown in the focus may have elective localizing power, and that small numbers of these are sufficient to cause lesions in animals corresponding to those in the patient. The experiments with emulsions of tonsils show that the degree of toxicity was proportional to the amount of infection in these organs.<sup>35</sup> On the basis of these experiments, the harm from foci of infection must be considered as being due to the absorption of toxic bacterial products, as well as to the entrance of the living bacteria into the circulation and their localization. The number of bacteria in acute lesions is sometimes so small as to be difficult to find and as to suggest that the specific lesions are due in part to the formation of toxic products. This possibility is also suggested by the observation that specific localizations occur with smaller doses of the broth culture directly injected than with the centrifuged bacteria resuspended in salt solution. The focus moreover may supply alien proteins, toxic or otherwise,<sup>37</sup> to which an individual as a whole, or the involved tissues such as joint structures, may have become highly sensitive. Clinical and experimental evidence,<sup>26</sup> of the possible occurrence of harm by this mechanism is not lacking.

The localizations following injection of the cultures from the case of mild myositis (Rabbit 3368) and from the case of acute iritis (Rabbit 3458) are in accord with the results obtained by Irons, Brown, and Nadler in their study on experimental iridocyclitis in rabbits and with the results I have reported previously. These results show that experimental iritis and myositis or arthritis are prone to occur simultaneously.<sup>38</sup> This was found to be the case following injection of strains isolated from rheumatic myositis and allied conditions, as well as of laboratory strains of streptococci when they had attained a certain grade of virulence from animal passage (38). Moreover, the results in animals are in harmony with those in persons who have

had repeated attacks of iritis and who are prone to have myositis and similar conditions. The occurrence of lesions in the fetuses similar to those that occurred in the mother (Rabbit 1700) is especially interesting. The amniotic fluid was sterile. No bacteria were found in normal tissues in the fetuses, while the tissues with lesions contained the streptococcus injected, and hence may be regarded as the result of embolic infection. This is a special indication of elective localization, since the bacteria must have passed through the walls of four sets of capillaries before they could lodge in the specific tissue. Specific localizations in the fetuses have been noted also in experiments in influenza. In this connection it should be mentioned that Curtis found that streptococci, associated with spontaneous abortion in women, when injected intravenously into pregnant rabbits, tend to lodge in the uterus and to produce abortion or absorption of fetuses. The view held by many obstetricians,<sup>46</sup> that foci of infection predispose to eclampsia, abortions, and to ill health of the fetus, would thus seem to have experimental basis.

The inability to obtain the specific localization at any one time in animals injected with bacteria from these foci should not necessarily be considered as evidence that a causal relationship might not have been present at some other time, for I have shown repeatedly that peculiar infecting powers may be lost in a focus just as in artificial mediums and from animal passage, a finding which Irons, Brown, and Nadler corroborate. The occurrence of lesions other than the specific ones in organs or tissues of animals injected with relatively large doses should not detract materially from the general truth of the elective localization theory, and should be looked on as evidence for, rather than against, causal relationship between focus and systemic disease. The non-specific lesions are usually relatively slight, roughly in proportion to the size of the dose, and may not occur if the dose is accurately gauged. They tend to occur in the same type of tissues in a series of animals. The tissues involved commonly correspond to those frequently affected in persons with certain diseases which are not demonstrably present at a given time, but which may become manifest later.

In a previous paper it has been shown that cultures from chronic foci of infection at the time of acute attacks of systemic disease, such as appendicitis, tend to reproduce the acute disease in animals, but that this may not be the case subsequently. This finding has been

interpreted by some observers<sup>22</sup> to mean that the organism in appendicitis enters the appendix from its lumen, passes into the blood stream, and on to the focus. This is conceivably possible in acute appendicitis but in other diseases, which must be regarded as of embolic origin, this interpretation would seem illogical. Experimental appendicitis follows intravenous injection of the proper strains, a fact which has been noted also by Helmholtz and Beeler,<sup>20</sup> but it has never been produced by placing the bacteria into the uninjured lumen of the appendix of animals. An acute exacerbation in the focus should occur if the bacteria from acute infections suddenly become lodged in the chronic focus, but such exacerbations do not occur. It is a well-established clinical observation that systemic invasion commonly occurs, not at the time of an acute attack of tonsillitis or of acute pulpitis, but some time after the acute symptoms have subsided, usually in from ten days to a month. It is during this time, as I have pointed out, that bacteria may acquire specific infecting power. The changes in the focus take place gradually and hence are not accompanied by evidence of acute exacerbation. Accordingly, the interpretation that the systemic disease is the result of embolic infection, whether aided or not by local predisposing factors, from a distant focus, would seem more true to fact.

Howe questions the significance of my experiments on the production of ulcer by intravenous injection of streptococci. He states:

"Bertram says that for half a century it has been recognized that a peptic ulcer forms when a circumscribed area of the stomach loses its normal resistance through malnutrition or neurosis to the digestive effect of the gastric juice, and is digested. Burge and Burge assert that decreased resistance of a circumscribed area of the stomach to gastric juice due to a decreased oxidative process of the cells of the area, followed by subsequent digestion of the area by pepsin, is the explanation of gastric ulcer."

These observations still leave the cause of the local disturbance undetermined. The results of my experiments indicate that the local malnutrition or neurosis described by Bertram, and the circumscribed area of decreased oxidation described by Burge and Burge, commonly are due to embolic localization of streptococci having affinity for the mucous membrane of the stomach.

The tendency to systemic invasion in acute infections about the teeth and jaws is recognized by all. Some observers have suggested that the rôle played in the causation of systemic ills by chronic localized infections about the teeth and jaws, particularly infected pulps,



apical abscesses, and granulomas, must be unimportant because nature's efforts are quite sufficient to protect the individual who harbors them; that the wall of connective tissue in a granuloma makes invasion of the blood stream by bacteria impossible or highly improbable; and that, since these conditions are so often free from symptoms, they must be harmless. In the light of the results of the experiments reported in this paper, this explanation does not seem tenable. It is a well-known fact that new blood vessels are formed constantly during inflammatory reactions following injury of tissue from any cause. It has been shown that the bacteria in granulomas and pulps of teeth occur chiefly where the connective tissue is highly cellular or embryonic in character, where leukocytic and round-cell infiltration is present, where new blood vessels are being formed, and adjacent to or within the larger blood vessels (Figs. 327, to 334, 348 and 349). It is evident, therefore, that the bacteria do not need to pass through a dense wall of connective tissue to enter the lymph or blood streams even in the most chronic conditions.

The close proximity of the bacteria to the blood vessels and to active lesions has been noted in recently infected pulps, in granulomas which had existed for from five to twelve years, and in infected pulps of animals injected intravenously a short time previously. The sclerotic connective tissue should be regarded as the result of a long-continued infective process which tends to protect the surrounding structures from bacterial invasion, but which has little power to prevent invasion of the blood or lymph streams. Indeed, by virtue of the density of the connective tissue, which allows no expansion, it might be regarded as tending to force the bacteria and their products during exacerbations of these infections along the line of least resistance into the circulation. It is not improbable that the plunger effect from mastication tends to drive the bacteria and their toxic products in apical infections in the same direction. Since pain in these areas is the result chiefly of pressure, the absence of this symptom should be regarded as evidence that free drainage, into the circulation, of the bacteria and their products is afforded, rather than as evidence of the harmlessness of these conditions. In the light of these findings, moreover, freedom from demonstrable systemic disease, often for long periods, in persons who harbor these infections may be considered to be due more to general resistance, to a natural or acquired immunity, than to a local protection from encapsulation of the microorganisms.

In order that an infection from septic foci may become established in remote body tissues, the same laws of resistance which afford protection against microbic invasion from other sources must be overcome. A focus of infection, wherever found—it may be in the intestinal tract, which, for mechanical reasons, can neither heal nor drain—that is teeming with microorganisms, should be regarded as a test tube with permeable walls imbedded in the tissues where absorption channels for bacteria and their products are present. In consequence, the play between the living bacteria and their products, and the protective mechanism of the host, becomes forced. A certain degree of immunity no doubt results, but since the bacteria (streptococci) usually present are poor antigens, the immunity induced is transient; and, since a state of increased susceptibility or hypersensitiveness from overstimulation may supervene, the protection may be inadequate. This is what occurs commonly during the immunization of horses and other animals with living streptococci, if the dose is not accurately gauged.

There is another reason why the mechanism of immunity may be inadequate to afford protection. By virtue of the gradation of oxygen pressure, and the presence of mixtures of bacteria in primary foci, the bacteria may change in immunologic characteristics and in infecting powers. In that case the antibodies previously formed would be valueless. Before antibodies which would react with the new strains could be formed, opportunity for invasion and the production of localized lesions by the changed organisms could occur.

It has been stated by some workers that the bacteria, especially streptococci, from chronic localized dental infections are avirulent, and therefore not to be considered of etiologic importance. If virulence is understood to mean the power of aerobic cultures of these organisms to kill animals by overwhelming infection following their injection, disregarding the fact that most of the diseases apparently due to focal infection remain localized and are not overwhelming infections, then this contention is correct; but, if virulence is taken to mean the power to produce lesions, as determined by careful necropsies in anesthetized animals, it does not hold. By the use of cultures grown under partial oxygen tension, we have found that the bacteria in many of these foci are pathogenic, in some instances markedly so, and that they tend to lodge and produce lesions in the tissues or organs of animals, corresponding to those involved in the patient

from whom the culture is taken. This finding is in accord with the rather common occurrence of acute exacerbations in these infections following various manipulations through the root canals in attempts at sterilization. The results with partial-oxygen-tension cultures lend some support to the view held by many that this phenomenon is associated in some way with the entrance of air or oxygen.

The importance of affording the bacteria in these experiments a gradient of oxygen pressure, and of injecting the bacteria soon after isolation, cannot be too strongly emphasized. The first consideration, in this study, has been to determine whether the foci contain living bacteria which can reproduce the disease in animals. If aerobic cultures only are made, no growth may occur in inclosed foci in which partial or complete anaerobes are present; or only nonpathogenic organisms may develop, as in open infections such as pyorrhea, in which a mixture is constantly present. Thus, negative results in animals injected with a pure culture, such as green-producing streptococci grown aerobically, have little value since it is quite likely that the parasitic strain failed to grow or that the property on which localization depends has been destroyed. By the use of methods embodying these principles, specific and other lesions have been produced with bacteria from the various types of dental focal infections such as gingivitis, pyorrhea, infected pulps, apical abscesses, discharging sinuses, and granulomas.

The tendency to produce lesions in the pulps of teeth in animals was more marked when bacteria from infected pulps were used than when they were taken from other dental foci or foci elsewhere. This was especially true if the pulp showed evidence of recent infection. In some instances, however, lesions resulted from the use of strains isolated from tonsils or other foci outside the dental field. In one case of recurring attacks of pyorrhea, injection of animals with cultures from the pus pockets, during an acute attack, caused hemorrhage and edema of peridental membranes. Parallel series of animals were injected with cultures from infected tonsils and various dental foci in many of the cases, and in some with cultures from the metastatic lesions as well. Usually the localizations were strikingly similar. The injection of the primary cultures of pus from tonsils and open infections about the teeth, such as pyorrhea, tended toward a wider range of localization than that which followed injection of cultures from enclosed infections about the teeth and about the metastatic lesions.

Lesions in the tonsils of animals were found in only a few instances, and only when the lymphoid tissue in other parts of the body was hemorrhagic. This finding is to be expected since the tonsils studied showed little evidence of inflammation, and since the infection in the pockets in these organs is really outside the tonsil proper. The injection of a single small dose was sufficient at times to produce the specific localization, but a fair sized dose should be injected before the result is considered negative.

In order to simulate the condition in the patient more closely, in that the bacteria would need to pass through a series of capillaries before reaching the specific tissue, in some of the diseases studied, intraperitoneal injections of cultures were made. Even this method was followed by elective localizations in some instances. In the experiments with pus from tonsils, a small number of the bacteria which had grown in the focus was sufficient for elective localization. In parallel experiments, which will be reported shortly in a study on myositis, cultures of pus from tonsils from normal persons and from persons suffering from metastatic disease show that the former may be harmless, and that the latter are prone to produce lesions in the tissues corresponding to those involved in the patient.

The identity of streptococci isolated from specific experimental lesions, following injection of cultures from foci of infection and the metastatic lesion, has been established in some instances. Improvement occurred in patients from whom foci were removed, which were proved to contain the specific organism at the time of removal. The organisms have been demonstrated in the lesions in animals, although absent elsewhere, by cultures and in sections.<sup>20,22,24,25</sup> Reinjection in animals produces characteristic lesions, and the organisms may again be isolated. Experiments with filtrates of the cultures have proved the absence of a filtrable virus. The requirements for the demonstration of etiologic relationship of extraneous parasites to disease have been fulfilled.

The results reported heretofore on elective localization of bacteria from foci of infection have been verified and extended. The findings warrant the conclusion that chronic foci of infection about the teeth are potentially or actually detrimental to the health of the persons who harbor them. The lesions which are more or less enclosed, and which drain only into the circulation, are probably the most dangerous and should be regarded as veritable experiments, which alone or in

connection with predisposing factors will sooner or later break down the resistance of the patient and produce disease. The harm from oral sepsis, according to the experiments with emulsions from the infected tonsils and with the bacteria in the pus from tonsils, may be due to absorption of poisonous bacterial products and to the living bacteria themselves. The places of localization of bacteria, aside from the influence of a lowered resistance, local or general, and from that of injury, fatigue, strain, improper food, bad hygiene, disease, and heredity, will depend largely on the peculiar infective capacity, or the peculiar poison-producing power, of the bacteria at hand.

#### CLINICAL FINDINGS

Let us consider the frequency of probably the most dangerous form of dental sepsis: pulpless teeth and blind abscesses. Howe reports the presence of 40,000 abscessed teeth in an examination of 50,000 children at the Forsythe Dental Infirmary, and points out that abscessed teeth must be of little importance as a source of infection since arthritis deformans (a disease which rarely occurs in childhood) was not observed. It is to be regretted that no information is given with regard to the condition of these children at the time of the examination, for example; or to the number who later suffered from malnutrition, hypertrophied and infected tonsils and adenoids, leading to malformation of the jaw, to defective teeth, and to deficient mental and physical development; or to the number who had appendicitis, endocarditis, and so-called "idiopathic" infections, fatal or otherwise, in which the teeth were not even suspected as being a possible source of these infections. Langstroth, in his studies of cases at the University of California Hospital, found chronic focal infections in 84 per cent of ulcer patients, in 66 per cent of subacute cases of arthritis, in 73 per cent of the chronic cases of arthritis, and in 100 per cent of the gallbladder cases. The acute and subacute cases responded well after removal of the foci, even to the point of absolute cure. In many of the chronic cases, the patients had less pain and no further progression of the disease. Duke in tabulating 1000 medical cases in which the patients suffered from some form of chronic disease, found a marked degree of oral sepsis in 66 per cent. Thoma<sup>49</sup> in a similar group of cases at the Robert B. Bringham Hospital in Boston found alveolar abscess in 88 per cent. Irons found alveolar abscess in 44 per cent in a series of 124 pa-

tients with miscellaneous diseases. Abscesses were present in 76 per cent of the arthritis group and in 47 per cent of the nephritis group. Black found that the peridental infections, without reference to complaint, were 56 per cent in persons under twenty-five years of age, 72 per cent in persons between twenty-five and thirty, 87 per cent in persons between thirty and forty, 89 per cent in persons between forty and fifty, and 100 per cent in persons more than fifty. Many of these infections are found in teeth from which the pulp has been removed artificially and the canals improperly filled, as is shown by Ulrich, who found that 68 per cent of all artificially devitalized teeth had apical abscesses; and that of 1350 so-called dead teeth examined, 83 per cent were abscessed. The number of persons suffering from diseases directly attributable to these infections, as well as from nonrelated conditions which have been cured or benefited by elimination of foci of infection in the various branches of medicine, is so large as to be quite sufficient to prove the general truth of the idea of causal relationship.

#### THERAPEUTIC SUGGESTIONS

The opportunity of the dental profession for coöperation with the various branches of medicine along these lines needs no emphasis. The prevention of oral sepsis in the future with a view to lessening the incidence of systemic disease should henceforth take precedence, in dental practice, over the preservation of the teeth almost wholly for mechanical or cosmetic purposes, as has been so largely the case in the past. Every effort should be made for the prevention of dental infections and for the elimination of those already present. Preventive measures should begin in childhood with a view to obtaining perfect development of the teeth and oral cavity, and thus preventing various defects which would later lead to sepsis. This calls for the coöperation of dentist, pediatricist, and throat specialist.

The principles underlying various procedures for the prevention and cure of infections of the gums and enveloping membranes about the roots of teeth may be regarded as fairly well understood and effectively applied by many. It should be emphasized, however, that the chief harm from these conditions comes from the absorption of the bacteria and their products into the lymph stream or blood, especially if drainage is inadequate, not from swallowing the infectious material, and that the infections predispose to embolic infections within and

without the dental field. The correction of pyorrhea and allied conditions is, therefore, of great importance.

Infections of the dental pulp, pulpless teeth, and apical abscesses are theoretically the most dangerous of the various forms of dental foci. They are usually free from symptoms and hence unsuspected. They are situated in osseous tissue which allows no expansion. They lack drainage other than into the circulation and are exposed to pressure transmitted by the teeth during mastication. They remain active and do not heal for a period of years; and the bacteria, as shown in this study, are not encapsulated as is usually assumed, but are found in areas of active inflammatory reaction where new blood vessels form and afford ample drainage into the circulation.

On the basis of these facts, there can be no doubt that the wholesale devitalization of teeth, often for trivial reasons, and the filling of infected root canals without due regard to asepsis, as practiced in the past, result in the formation of numerous apical infections, and in much ill health. The instances of cure or improvement in systemic diseases directly attributable to these infections and in non-related conditions are so numerous, that the procedure as practiced heretofore should be regarded as a veritable experiment.

It is a well-known fact in bone surgery that no amount of antiseptic treatment will cure an osteomyelitis unless all dead tissue is removed and the dead spaces are eliminated; if this is done, healing occurs promptly without antiseptic treatment. In the filling of root canals the removal of every particle of pulp tissue is recognized as a prerequisite for successfully preventing subsequent infection. Is there any reason to believe that, if the small amount of dead albuminous matter in divergent or tortuous canals leads to reinfection,<sup>46</sup> the larger amount in the apical region would not likewise become infected even though completely sterilized by ionization or other similar treatment? Hence it is doubtful whether any form of medication through the root canal, which would be applicable in routine practice, can be relied on successfully to sterilize the infected areas about abscessed teeth, and to prevent the areas from becoming reinfected. The fact that acute infections of the jaw occur not infrequently following these attempts is a further obstacle to the success of this method. Apicoectomy, while no doubt successful in removing the infection in the jaw in some instances, is applicable in only a small number of cases, and as a rule should not be attempted in persons who are ill from

secondary systemic conditions. The removal of infected pulpless teeth, together with the infected peridental tissues therefore seems to be the safest and surest means available at present for the cure of these conditions. The many ingenious devices applicable to vital teeth will do much in making useful masticating surfaces and agreeable cosmetic effects.

It is becoming more and more apparent that the lack of improvement in systemic disease following the extraction of one or more infected teeth, barring other foci, may be due to the fact that the peridental infection was left or was only partially removed; also that the occurrence of acute exacerbations following extraction and curettage is commonly due to this cause. Persons who have had all their teeth extracted may still harbor localized areas of infection in the jaws. Simple extraction is not sufficient. The importance of eliminating dead spaces in curing infections of bone in other parts of the body—a lesson learned during the war— lends support to the idea of the “surgical removal” of infected teeth.

Removal would seem to be the method of choice in cases of extensive apical infections. If a person who is perfectly well has harbored for some years one or more devitalized teeth in which the x-ray findings are negative, there would seem to be no good reason for extraction. If, on the other hand, the person is suffering from arthritis, a heart or kidney affection, or some other form of disease for which other causes cannot be found, such teeth should be removed. Owing to the reparative power of the cementum, it would seem possible to devitalize teeth safely whose pulps are sterile and whose canals may be properly filled, provided the operation is done in an aseptic manner. This should be done after the removal of other sources of infection, and only in teeth of vital importance for restorative needs. The somewhat lowered resistance to infection of the peridental tissues about non-vital sterile teeth may be more than counterbalanced by the removal of the pulp, since most infections of otherwise sound teeth no doubt occur through this organ. In case of beginning infection of the pulp from decay which has not yet extended into the periapical tissues, attempts at sterilization, and, if necessary, removal of the pulp and filling the canal may be justified in some instances, but not until cultures have proved that the tissues are free from living bacteria; and only if the responsibility is shared conjointly by patient and operator.



In the matter of eliminating foci of infection in the mouth and throat, the infections about teeth should as a rule be corrected first.<sup>44</sup> Tonsillectomy as now so commonly practiced before the condition of the teeth has been corrected is illogical. The lymphatics of the mouth and jaws drain into the tonsils. Some infections of tonsils improve or even disappear following the extraction of infected teeth. The unnecessary sacrifice of vital teeth should be condemned. Barker states:

"I do not think a tooth should be sacrificed unless indications are clear for its removal. I would urge you not to give widespread orders to extract teeth unless they are so diseased that they must come out. On the other hand, please do not try to save teeth that cannot be made aseptic, for there is real danger that they may injure the rest of the body."

A patient who is suffering from a serious disease of focal origin, after due consideration of other factors for or against extraction of infected teeth, should be given the benefit of the doubt even when the evidence is not conclusive that the responsible focus is contained therein. Extraction will do no harm, although inconvenient at the time, while non-extraction may result seriously.

"Not too much should be expected from the removal of a focus, especially in chronic conditions, because a similar condition may be present in inaccessible foci and in others too small to be detected. Moreover, recovery may be made difficult by local tissue sensitivity or peculiar mechanical conditions, and living bacteria in a metastatic lesion may continue the process independently of the focal source."<sup>45</sup>

The administration in guarded dosage of a properly prepared vaccine from a focus, following its removal, may be an important aid in overcoming the metastatic condition. But this or other forms of specific therapy cannot take the place of the eradication of the focus. It need hardly be pointed out that the prevention and cure of dental and other foci of infection is only a part of the problem. The conception of the problem of focal infection must not be too mechanical, for, as has been emphasized previously,<sup>44</sup> and again demonstrated experimentally in this study, the invasive power of the bacteria is extremely important. The elimination of visible foci would not eliminate all systemic infections, for as the invasive power of the bacteria increases, the need for forced entrance, as occurs from a focus, becomes less marked and thus the bacteria may gain entrance through the unabraded mucous membranes, as in the acute infectious diseases.

But even here, the broken continuity from localized infections predisposes to these diseases.<sup>43,46</sup> The importance of hygiene, of a properly balanced diet, and of the general health, and hence the coöperation between the various branches of medicine and surgery, including dentistry, needs hardly be emphasized.

A careful study of the clinical and experimental data now available seems to show conclusively that a sane and comprehensive effort toward the prevention and cure of septic foci in the dental and other areas will result in the alleviation of human suffering, in a better preservation of the tissues in old age, in a longer average duration of life, in increased mental and physical efficiency, in the prevention and cure of acute and chronic disease, and, through the laws of heredity, make for a sturdier race.

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# TONSILLECTOMY IN MYOSITIS AND ARTHRITIS

## Results in Two Hundred Consecutive Cases\*

H. I. LILLIE AND H. R. LYONS

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That the tonsil is a focus of infection in cases of myositis and arthritis is common knowledge and will not be discussed in this report, which deals with the results of operation in a series of consecutive cases of myositis and arthritis.

As a preliminary to the selection of the 200 cases of the series, letters of inquiry were sent to 400 patients who had been operated on consecutively. The answers from the first 200 were accepted as sufficient data for the basis of our report.

The data recorded were facts concerning sex, age, first attack of myositis or arthritis, number of attacks, joints involved, presence of pyorrhea alveolaris or tooth abscess, history of tonsillitis, history of previous tonsil operations, and the present condition, whether ambulatory, incapacitated, or invalided.

In recording the improvement in the long standing cases we fully appreciate the importance of the time element, and also the fact that in many other cases patients may improve without treatment. The series includes, however, all types of cases, from the very mild myositis to the very severe deforming arthritis that is strictly of an infectious origin. The gonorrheal and syphilitic types are excluded.

### DISCUSSION OF TWO HUNDRED CONSECUTIVE CASES

All of the 200 patients in the series were operated on between July 1, 1917, and Dec. 31, 1917. Letters of inquiry with regard to the final results were sent in November, 1918; thus ample time was given for improvement, although undoubtedly in a few cases there would have

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been further improvement had more time elapsed. Our percentages are, therefore, from this standpoint alone, too low rather than too high.

Eighty-seven of the patients were thirty years or less, and 113 were thirty-one years or more. The average age was thirty years. Seventy-one (81.6 per cent) of the first group of 87 patients were better after tonsillectomy; the others were not improved. Eighty-eight (77.7 per cent) of the second group of 113 patients were better after tonsillectomy; the others were not improved. These percentages indicate that as the condition becomes more chronic less benefit is derived from tonsillectomy, although in the long standing cases improvement is found almost as often as in the recent or subacute cases.

The average age of the patients who reported their condition worse was forty years. The duration of the myositis or arthritis in all the cases varied from a few days to thirty-nine years. The average duration of the myositis or arthritis in patients improved by tonsillectomy was eight years.

The 10 patients in whom the condition was chronic and who were invalids at the time of operation report results as follows: Two patients who were confined to bed were the same after tonsillectomy. Four walked but were incapacitated for work; ultimately 2 of these were better. Two were wheel-chair cases; one was better and one the same. Two had had to use crutches; one was better and one was not improved. Thus 4 of the 10 patients (40 per cent) reported improvement.

In the cases of arthritis, the joints involved in the order of frequency were the knees, the hands, the ankles, and the hips. In the cases of myositis, the shoulders and arms, the back, the lower extremities, and the neck were involved.

In the cases of pyorrhea alveolaris or tooth abscess, demonstrated both clinically and by the roentgen ray, 81.4 per cent of the patients were better after tonsillectomy; 36 per cent of these had dental work done in addition to tonsillectomy, and 45.4 per cent had no dental work done; 18.6 per cent of the patients were the same after tonsillectomy; 12 per cent of these had dental work done in addition to tonsillectomy, and 6.6 per cent had no dental work done.

PERIOD OF ONSET OF DISEASE	NO.	PER CENT.
Between 1915 and 1917.....	79	49.6
Between 1910 and 1914.....	33	20.9
Between 1900 and 1909.....	37	23.2
Between 1890 and 1899.....	7	4.4
Between 1879 and 1899.....	3	1.8

It will be noted that in a considerable percentage of the cases in which a diagnosis of pyorrhea alveolaris, dental abscess, or caries was established, the dental sepsis had been disregarded, and it is fair to assume that even a larger percentage of the patients had a possible focus of infection in their teeth and needed dental care. Too much emphasis cannot be placed on the importance of the care of the teeth as an aid to the cure in these cases. When patients who are examined by us present definite, marked dental sepsis and septic tonsils, we insist on having the teeth properly cared for before tonsillectomy is done.

The size of a tonsil is of variable importance in advising tonsillectomy. In the Mayo Clinic, reports and advice regarding tonsils are based on three main factors: (1) the result of properly expressing tonsillar crypts with a tonsil explorer; (2) the tonsil history; and (3) the patient's symptoms. The size of a tonsil is estimated on a scale of 1 to 4; 1 represents the submerged tonsil, 2 the tonsil that is just visible, 3 the tonsil presenting in front of the tonsillar pillars, and 4 the very large obstructing and pendulous tonsil. In the present series the average size was 2, those just visible in the cursory examination of the throat. This is the type that many physicians, specialists as well as internists, look on as harmless, and accordingly advise against a tonsillectomy. As a matter of fact the importance of the tonsil as a focus of infection does not increase with its size, nor has it any relation to it. In our cases the tonsillar crypts were carefully examined and an exact history taken both of the throat and of the general complaint before advice was given as to the probability of the tonsils being the focus of infection. A conservative position was taken in every case. In 6 per cent of the 200 cases a tonsillectomy had been attempted elsewhere, and in each case the myositis or arthritis continued as before, thus showing the value of a clean tonsillectomy in all cases.

One hundred fifty-four of the 200 patients were unable to work, or at least were unable to work steadily at the time of their examination. After tonsillectomy, 118 (77 per cent) of these were able to work steadily. Thirty-five (22 per cent) were the same postoperatively. Thirty-five patients of the series needed the help of crutches or a cane. Twenty-five (71 per cent) of these were enabled by the tonsillectomy to discard any help. Ten (29 per cent) were not benefited.

Opinions have varied with regard to the end-result in cases in which an immediate reaction was experienced after a tonsillectomy because of an acute attack of myositis or arthritis. Twenty-four

(12 per cent) of the patients reported an acute exacerbation of their condition immediately after the tonsillectomy. Nineteen (79.1 per cent) of these reported ultimate improvement; 5 were not improved. It is also noteworthy that of 159 patients who reported that they were better, 87 (55.3 per cent) reported that their improvement started immediately after the tonsillectomy; the average length of time before improvement began was eight weeks.

Ninety-two of the 200 patients had enlarged joints. Of these, 50 (54.3 per cent) reported that their joints had returned to normal size after tonsillectomy, and 45.7 per cent reported that their joints had remained the same. However, in a number of cases of long standing chronic arthritis with enlargement of the joints, the immediate results of a tonsillectomy have been surprisingly good. In many instances of long standing painful and enlarged joints, the joints have immediately decreased in size and become useful. We have had a number of patients who went to the hospital for operation using crutches or a cane, who were able to discard them thirty-six hours later.

Thirty-three of the patients had had treatment other than tonsillectomy, for example, massage, baths, electric vibration, phylacogens and osteopathy.

In the entire series only 57.7 per cent of the patients gave a history of tonsillitis. This is of interest in view of the fact that many practitioners believe tonsillectomy should be advised only when there is a history of tonsillitis or quinsy. In addition to the patients who did not give a history of tonsillitis are those who did not have a tonsillitis followed by an acute arthritic attack. It is obvious, therefore, that a tonsil need not be periodically inflamed in order to become a focus of infection, and it is even less necessary that an attack of tonsillitis should immediately precede the acute attack of arthritis.

The foregoing data constitute the general findings in the patients who present themselves for examination. The cases vary from the very mild up through each succeeding grade of severity to chronic arthritis and invalidism. The average of the sum total, therefore, represents the results obtained in all cases.

#### TWENTY-EIGHT SELECTED CASES

A special study was made of 28 selected cases in which there was a severe form of chronic infective arthritis with marked involvement of the joints. In some of these, definite roentgen-ray



findings were noted. The postoperative time element is identical with those of the other cases in the series. The average age patients was thirty-seven years; the duration of arthritis was from ten months to eight years; the average duration of arthritis in those who were improved was eight years; the duration in those who remained unimproved was from eight months to twelve years. Sixteen (56.1 per cent) reported their condition better, and 12 (42.9 per cent) were not improved. Seventeen of the patients were aged thirty-one years or more, of whom 9 (53 per cent) were better postoperatively, and 8 (46.3 per cent) were not improved. Eleven were aged thirty years or younger, of whom 8 (72.7 per cent) were better after operation, and 4 (36.3 per cent) were not benefited. The size of the tonsil was 2 in all but 6 of the cases.

It may again be noted that most of the patients in the series of 200 cases who did not obtain relief from tonsillectomy fall into the group of the long standing, chronic cases, and that in cases in which the arthritis was not improved after operation, six times as many of the patients were thirty-one years or more as were thirty or less. Even in the group of the severe type of arthritis, 53 per cent were of the older patients. Seventy-two and seven-tenths per cent of the younger patients in the group were markedly improved.

Twenty-one of the 28 patients were disabled or unable to work at the time of examination. Eleven (52.3 per cent) of these reported that their condition was improved and that they were able to work; the other 47.7 per cent were still incapacitated. Five (31.2 per cent) of the 11 who were improved reported that their improvement started immediately following the tonsillectomy. The average length of time before improvement was noticed was three months. In order to determine more exactly the results obtained in these 28 cases, they were classified into four groups:

Group 1.—The mild type of cases in which there was a history of repeated joint enlargement that receded, and the patient reported for examination in the interval stage.

Group 2.—Cases in which there was definite joint enlargement with the accompanying symptoms and signs, but without joint changes noted by the roentgen ray.

Group 3.—Cases in which there was marked joint involvement of a chronic nature, and slight roentgen-ray findings, such as fibrosis of the

joint capsule, or a beginning thickening of the bone on the articular surfaces.

Group 4.—Cases in which there was not only marked and long standing joint enlargement but also in which the roentgen ray showed definite signs, such as marked increase in bone on the articular surfaces, typical spine-like processes on the vertebral articular surfaces, or the destruction or osteoporosis of the articular borders.

Twenty-two of the 28 patients had enlarged joints before tonsillectomy was performed. Of this number, 6 (27.2 per cent) reported that their joints had returned to normal size; the others reported no change. Four of these cases fall into Group 1 and 2 into Group 2. It is a striking fact that in the patients who had been practically invalids with chronic arthritis, and in whom no changes were found by the roentgen ray, the joints returned to normal size and function in a relatively short time, and conversely that the patients in Groups 3 and 4 had no beneficial change in the joint involvement. This distinction of type is paramount when the end-results are considered in detail. It should be remembered that it is the patients classified in the first two groups who are given a practically hopeless prognosis and little or no chance for improvement by most physicians.

Six (21.4 per cent) of the 28 patients reported an acute exacerbation of the joint signs and symptoms immediately following tonsillectomy. Three of these eventually reported improvement; the others were not improved. An acute flare-up or exacerbation postoperatively may be hailed as a sign that the tonsils were the active focus of infection. The end-results in these severe types of arthritis may not be entirely encouraging to the patient. Eleven (39 per cent) had some form of dental work done in addition to their tonsillectomy. Nine (81.1 per cent) reported their condition better; two were not improved. It may be assumed that many of these patients retain teeth that are acting as a focus of infection, and that a higher percentage of improvement would undoubtedly be reported if the roentgen ray were employed, and a careful examination were made in every case, so that all dental sepsis might be removed promptly and thoroughly.

## SUMMARY

1. It is justifiable to advise a tonsillectomy in every frank case of myositis or arthritis.

2. A marked improvement may be assured from tonsillectomy alone in 79 per cent of all cases.

3. It is necessary to remove all possibility of dental sepsis; by so doing a larger percentage of patients will be improved.

4. The duration of the myositis or arthritis is a factor in the ultimate results, although benefit and even complete cure is obtained in some long standing, chronic cases.

5. Forty per cent of the patients with chronic myositis or arthritis who are invalids will respond favorably to tonsillectomy.

6. The size of a tonsil has no bearing on its possibility as a focus of infection. A careful expression of the tonsillar crypts and a history of throat trouble associated or not associated with the myositis or arthritis is essential in the diagnosis.

7. An absence of a history of diseased tonsil in no way eliminates the organ as a focus of infection.

8. A clean tonsillectomy, with the removal of the plica tonsillaris, is necessary in every case.

## ANGIOMAS OF THE LARYNX: REPORT OF THREE CASES\*

G. B. NEW AND C. M. CLARK

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True angiomas of the larynx are unusual. They may occur primarily in the larynx but more often they are associated with similar conditions about the face and mouth and of the upper air passages. Histologically the tumors are divided into two types: (1) hemangiomas and (2) lymphangiomas. Pseudo-angiomas may be included as a third type in a consideration of angiomas in general. Hemangiomas are subdivided into two types, simple and cavernous. Pseudo-angiomas include the varices and the various lymphectasæ.

Several cases are reported in the literature as true vascular tumors in which the clinical picture indicates some form of varix or an organized clot in a fibroma or a polyp. Fauvel, in 1876, reported 2 cases of true angioma of the larynx. We have found no evidence of cases previous to this time. Fauvel also described a third case in which the tumor was manifestly papillary but the vessels were so dilated that they formed veritable lacunar spaces which resembled true hemangioma; a definite diagnosis was not made in this case. Since that time a number of cases have been reported, and described as probably angioma, but sufficient clinical and microscopic evidence with which to make a definite diagnosis was lacking. Wolfenden, in 1888, reviewed the literature and found 12 cases, to which he added one of his own. In 1895 Koschier recorded a case of lymphangioma, the first we were able to find up to that time. Mayer, in 1916, reviewed the literature carefully and reported 41 cases, including 2 of his own, but he did not differentiate the types. He verified 12 of the 41 cases mentioned in his article. Richardson, in 1917, contributed an article in which he reported one case of lymphangioma of the larynx. This is the only case of the kind we have been able to find reported in the American literature, although several have been recorded by European writers.

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*Incidence.*—In the 52 cases of true angiomas reviewed in the literature a conclusive diagnosis was reached in each case either by clinical or microscopic examination. The 3 cases observed in the Mayo Clinic added to this group make 55 cases.

Forty-four cases of hemangioma and 8 cases of lymphangioma have been recorded. The relative incidence of true laryngeal angiomas is small, as indicated by the finding of only 8 hemangiomas and no lymphangiomas in a series of 217 true laryngeal neoplasms observed in the Mayo Clinic. Table 1 summarizes the findings in the cases of angiomas collected from the literature and from our files.

*Age.*—The youngest patient having a hemangioma was ten weeks (Levbarg's case); one of our patients was eleven weeks. The oldest patient was sixty-two years (Loomis).

#### HEMANGIOMAS

Patients under 20 years.....	6
Patients between 20 and 30 years.....	5
Patients between 31 and 40 years.....	5
Patients between 41 and 50 years.....	5
Patients between 51 and 60 years.....	5
Age not stated.....	21

#### LYMPHANGIOMAS

Patients 16 years.....	1
Patients 28 years.....	2
Patients 40 years.....	1
Patients 48 years.....	1
Patients 55 years.....	1
Age not stated.....	2

*Sex.*—Twenty-two of the 47 patients with hemangiomas were males, 10 were females; in 15 case reports the sex was not given. Our 3 patients were females. According to Mayer angioma of the larynx occurs approximately twice as often in males as in females. Five of the 8 patients with lymphangioma were males, 2 were females; in one case the sex was not given.

*Symptoms.*—Angiomas of the larynx are believed usually to be congenital. The symptoms are similar to those of any other benign laryngeal neoplasm but they vary in intensity according to the size and character of the tumor. It is the general impression that angiomas do not increase in size after the patient is ten years of age. Our tabulation shows that the symptoms occur most often after the age of 20 which would indicate some exciting cause as a factor.

Hoarseness is most often the first symptom complained of; it may be intermittent, especially in cases of true angioma without solid tumor formation, or it may gradually increase over a period of years till finally speech is lost. Complete respiratory obstruction is not often seen in these cases because of the relatively small size of the growth, but when it occurs tracheotomy usually is necessary.

Some of the patients have recurring attacks of hemorrhage which may result fatally, as happened in a case described by Ferrari. In case an intralaryngeal examination has not been made hemorrhage may be the first symptom to suggest angioma. The severity depends a great deal on the vascular qualities of the tumor as well as on the coagulability of the patient's blood.

Bioggi, in 1916, reported a case at the Eighth Congress of the Italian Society for Laryngology in a hemophiliac aged 42. The tumor was expectorated spontaneously; a severe hemorrhage followed which was checked by gelatin enemas.

Blegvad, in 1908, reported a case in the Proceedings of the Danish Oto-Laryngological Society. The patient came for observations because of sudden expectoration of blood fourteen days before; hoarseness had existed for several months. The tumor was the "size of a millet seed." Microscopic examination revealed a true hemangioma.

Levbarg, in 1918, reported a case in a baby ten weeks old in which the first laryngeal symptom was severe dyspnea, but the child had had paralysis of the upper left extremity since birth, also small angiomas on the left temporal region, hard palate, uvula, and neck.

Ryerson, in 1912, reported a case in which the patient had difficult and oppressive breathing, without hoarseness or cough. Brown reported the case of a patient who complained of an uneasy sensation on the right side of the larynx for three weeks without other symptoms. One of the cases reported by Fauvel demonstrated the occurrence of intermittent hoarseness which sometimes is found with cavernous angiomas.

Pain is very infrequently associated with benign neoplasms of the larynx, unless a secondary infection is present. Chiari's case is the only one of angioma in which pain was the chief complaint. All but two of the cases reported were either suspected or definitely diagnosed during life. Loomis' and Phillips' and Ruh's cases were found at necropsy.

The shortest duration of symptoms was three weeks; one patient was hoarse for nine years before a diagnosis was made.

*Location of the tumor.*—Angiomas of the larynx, when associated with similar conditions elsewhere, may involve the extrinsic structures as well as the intrinsic, but when localized in the larynx are most frequently found in the true and false cords. In a few cases more than one laryngeal structure was involved by a single growth.

#### STRUCTURES INVOLVED IN 47 CASES OF HEMANGIOMA

Right cord.....	8	Right ventricular band.....	6
Left cord.....	9	Left ventricular band.....	4
Both cords.....	5	Right arytenoid.....	2
Anterior commissure.....	3	Left arytenoid.....	2
Right hyoid fossa.....	1	Subglottic area.....	7
Mucous membrane of larynx from cords down to third tracheal ring.....	1		

One of our patients, a baby eleven weeks old, had a cavernous hemangioma over the scalp and nose, associated with the laryngeal tumor.

#### STRUCTURES INVOLVED IN 8 CASES OF LYMPHANGIOMA

Left arytenoid epiglottic fold.....	1
Right cord.....	2
Left ventricular fold.....	2
Right arytenoid epiglottic fold.....	1
Right false cord and right aryepiglottic fold.....	1
Cord (side not stated).....	1

*Clinical Findings.*—The macroscopic picture of all true laryngeal hemangiomas is about the same; also all lymphangiomas present a characteristic clinical picture. The pseudo types vary according to the kind of tissue predominating if it happens to be part of a degenerative change in a solid neoplasm, or if it is a varix, according to the size and number of vessels present.

A true cavernous hemangioma is the most frequent type and varies in size from 0.2 cm. to 2.5 cm. It may be found attached to one or more laryngeal structures, always of a dark bluish or purplish color, rarely pulsating (Fig. 357). A few cases of true cavernous hemangiomas are reported as pedunculated, but usually they have a broad flattened base. The chief clinical characteristic is a bluish dark colored tumor, smooth surfaced, which feels soft, flattens out or decreases in size on pressure with a probe. Loomis and Ryerson describe multiple cavernous hemangiomas.

Simple or superficial angiomas are usually of the same color as the cavernous types but a few are bright red. They have no tumor formation, simply being a flattened vascular structure confined to the mucous and submucous tissues. Examination with a probe in this type is of little value. These tumors are often more extensive than the cavernous type, sometimes involving almost the entire larynx and part of the trachea.

Lymphangiomas may have a smooth or papillary surface; they are relatively larger than the hemangiomas. According to Harmer they are pale and transparent (Fig. 359). On examination with a



FIG. 357 (Case A131602).—Angiomatous polyp and cavernous hemangioma.

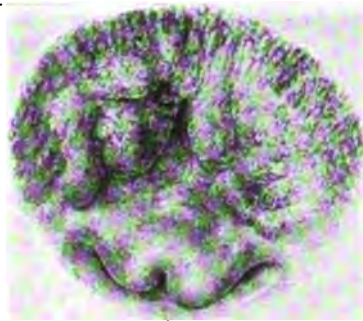


FIG. 358.—Lymphangioma taken from Harmer's article.

probe the tumor offers more resistance than the hemangiomas. According to the cases reported lymphangiomas are single; sometimes a lobulated tumor appears as two distinct growths.

The varices present a tortuous clump of vessels, often pulsating, usually a brighter red than angiomas. Clinically it is often hard to differentiate a simple varix from a simple or superficial hemangioma, while the cavernous types are distinctly characteristic.

*Diagnosis.*—Most cases reported in the literature have been diagnosed necessarily from a clinical examination, especially in cases of children, when it is difficult to get the required data. Because of the similarity between true hemangiomas and the pseudo types, a clinical diagnosis is not always correct. A microscopic examination is essential to an absolute and accurate diagnosis. In the lymphangiomas a



correct percentage of clinical diagnoses would be much larger than in the hemangiomas. We believe that all the cases reported in which a microscopic examination was not made should be classified according to the author's opinion, unless the description points conclusively to some other condition. If a laryngoscopic examination can be made there should be very little difficulty in differentiating true angiomas from malignancies of the larynx.

It is undoubtedly true that all laryngeal neoplasms are associated, in some way, with continuous irritation of the larynx. Granting that true laryngeal angiomas are congenital, the majority manifest themselves between the second and fifth decades of life. The first symptoms may be noticed suddenly following an acute exanthema or the onset is gradual, most often associated with a chronic inflammatory condition of the upper air passages.

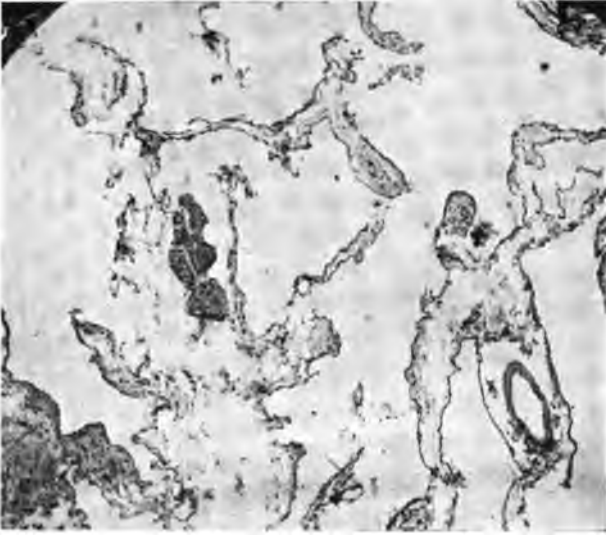
So far as we know there is no definite association with other general pathologic conditions. In one of our cases in which the growths, two in number, were attached to the left side of the anterior commissure and the left arytenoid respectively, we found tuberculosis in the upper right lobe, and dilatation of the arch and descending aorta. Many case reports contain no general findings. In another of our cases, the blood chart showed 20 per cent hemoglobin, 3,002,000 red cells, 7600 leukocytes, polynuclear neutrophils 14.5 per cent, large lymphocytes 10.0, small lymphocytes 66.5, eosinophils 8.5, basophils 0.5; anisocytosis was marked, poikilocytosis and polychromatophilia were slight; this was a case of secondary anemia in a baby aged eleven weeks. In our third case all general findings were negative.

Symonds' patient contracted syphilis ten years before his examination. The first symptom noticed by him was hoarseness which improved when he took potassium iodid. In Phillips' and Ruh's case the onset of symptoms followed an attack of measles. McKinney's patient had primary lues four years before his examination, followed at different times by secondary manifestations including paralysis of the left arm. Levgarg's patient had had paralysis of the left upper extremity since birth.

*Pathology.*—Simple hemangiomas consist of newly formed capillary blood vessels with either thin or thickened walls, and surrounded by a stroma of connective tissue.

Cavernous angiomas are made up almost entirely of a new growth of tissue composed of various shaped blood spaces lined with endothe-

lial cells. They vary in size and usually are found surrounded by large quantities of fibrillar connective tissue containing small quantities



**FIG. 359 (Case 131602).—**Photomicrograph taken from tissue removed from hemangioma.



**FIG. 360.—**Lymphangioma taken from Menzel's article.

of smooth muscle tissue (Fig. 359). The tissue is dented with alveoli which communicate with one another. The blood in these alveoli retains its normal qualities.

Pseudo-angiomas consist of dilatations or enlarged spaces in pre-existing vessels of normal tissues, or may sometimes be found as part of the vascular structure of a benign neoplasm.

Lymphangiomas involve the lymph system. Their chief characteristic microscopically consists of new growths filled with dilated lymph spaces; these spaces are lined with endothelium and are supposed to originate in new formed lymph channels. In most cases in which tissue was available a substance resembling true lymph was found. Varying amounts of connective tissue have been found between the vessels; in some places they seem to be almost in direct contact (Fig. 360).

*Treatment.*—Various methods of treating angiomas have been reported. Wolfenden believed the danger from hemorrhage to be so great that he advised no interference unless great difficulty in respiration developed. Angiomas, like other laryngeal neoplasms, sometimes require a tracheotomy to relieve the dyspnea. Intubation in such cases is not safe because the trauma associated with such procedures is likely to produce severe hemorrhage.

Ryerson was the first to use radium in the treatment of a laryngeal angioma. We have used radium in two of our cases with excellent results and believe it is a specific for all true vascular growths of the larynx, as well as other parts of the body. The pseudo-angiomas, such as fibromas with vascular formations, do not respond so well to radium. This type, if the growth is small and pedunculated, can usually be removed with laryngeal forceps by the indirect method.

True angiomas or nodular pseudo-angiomas, if small, can often be satisfactorily treated by fulguration, or the electric cautery. Radical operations, such as thyrotomy with or without the cautery, should never be done except when all other methods fail to relieve the distressing symptoms, or in cases of large angiomas in which the danger of hemorrhage from removal is great. The method of choice in treating all laryngeal angiomas is suspension laryngoscopy and inserting radium directly against the tumor. In case operation is decided upon in patients with large angiomas, thyrotomy with or without the cautery is preferable; it insures the best exposure and danger from hemorrhage is reduced to the minimum.

## REPORT OF CASES

**Case 1 (180247).** A girl aged nine months, was examined in the Mayo Clinic Dec. 12, 1916. When the child was three months old the parent had noticed a rattling in her throat and difficulty in breathing which grew worse at night; the breathing might be described as an inspiratory stridor. She had some difficulty in swallowing. She had a slight cough and recurring attacks of vomiting. The urinalysis and the x-ray of the chest were negative.

The laryngoscope revealed a dark bluish tumor in the left subglottic region bulging to the middle of the trachea. The mucous membrane was smooth, and the tumor was sessile with dimensions approximately 1.25 cm. by 1.875 cm. The diagnosis was made from the history and the clinical examination.

The child's symptoms did not demand immediate relief so we decided to use radium. Jan. 30, 1917, a 50 mg. tube was applied outside the larynx for five hours with 2 mm. of lead screening and 2.5 cm. of wood distance. The child had improved considerably when last heard from, but we have been unable to learn the ultimate outcome of the case.

**Case 2 (131602).** Mrs. J. J., aged 45, came to the clinic May 25, 1915, complaining chiefly of rheumatism in her legs, which had developed four years before. The patient also had pain in the chest which radiated to the shoulders and arms. Hoarseness was first noticed fourteen years before and for several years was intermittent, but she did not consider this of any consequence. Two years before her examination she lost her voice completely; since then the hoarseness had been constant. There was no dyspnea, no expectoration, and no hemoptysis; the Wassermann test was negative. The x-ray of the chest showed marked bronchial thickening, tuberculosis of the right lobe, and dilatation of the arch and descending aorta.

Indirect examination of the larynx disclosed a small sessile tumor about the size of a pea, attached to the left arytenoid cartilage. It was dark blue, smooth, not pulsating, and when examined with a probe a deep indentation could be made. A small tumor was found attached by a pedicle to the anterior commissure filling the anterior two-thirds of the glottis. It was a bright red, and resembled a polyp more than a cavernous hemangioma. Because of the large size of the tumor an external operation was decided on. June 1, 1915, thyrotomy with cautery was performed (E. S. Judd). Tissue from the pedunculated tumor showed an angiomatous fibroma. The small sessile growth microscopically showed a structure similar to a true cavernous angioma (Fig. 357).

**Case 3 (90363).** A baby girl, eleven weeks old, was examined at the clinic Aug. 20, 1913. The child had been hoarse for five weeks, and since then had been gradually getting worse. Dyspnea was marked. The child cried only with great exertion; a slight cyanosis had appeared one week before, and she had vomited at intervals.

Examination showed a cavernous angioma on the right side of the nose, a small one 1.25 cm. by 1.25 cm., in the right inner canthus and one over the left breast and one over the scalp. The larynx was not examined. The hemoglobin was 20 per cent; the red cells were 3,030,000 and the white cells were 7,600. The x-ray of the chest was negative. Because of the blood picture albuminate of iron was added to the milk feedings. Aug. 22, 1913 intubation was performed at Dr. C. H. Mayo's suggestion and the tube was left in place for sixty-eight hours. Marked dyspnea followed the removal of the tube, but respiration improved gradually. When the child was examined again Sept. 2, 1913, she was breathing normally, and there was very little hoarseness. At this time radium was applied over the larynx, also to the angiomas over the face and scalp. Oct. 24, 1913, the patient had gained four and one-half pounds in

weight, and wheezed only slightly during respiration. Radium was again used. When the patient was last seen, Dec. 16, 1913, all symptoms had disappeared; the angiomas over the face and scalp were hardly noticeable, and the hemoglobin had increased to 35 per cent. We have recently heard from the mother who says the child is having no trouble.

The first indication in this case was the immediate relief of the dyspnea, and as the intubation relieved the distressing symptoms it did not seem wise to make a laryngoscopic examination. Our diagnosis, therefore, was made from the clinical history, and the association with true cavernous angiomas in other parts. As true angiomas are supposed to be congenital, the occurrence of laryngeal obstruction in such a young child, with other findings, and the fact that improvement in the symptoms followed the use of radium would strongly indicate a similar growth in the larynx.

#### REPORT OF CASES IN THE LITERATURE

A few cases have been recorded, which in some respects resemble true angiomas, but we have not included them in our tabulation either because the authors did not report them as true angiomas, or because of insufficient description.

Johnson, in 1865, reported a "vascular cyst" occurring in a man of 50; it was located in the anterior commissure.

Fourine, in 1867, found a "melanotic growth" on the epiglottis. Fourine is quoted by Heinze, whose article we read, but no description of the case is given.

Hooper, in 1884, described a case of nodular, sessile, bluish neoplasm on the left cord. Microscopically it showed loose connective tissue, with large spaces full of blood and altered fibrin. The connective tissue was edematous and highly vascular, with no true organization of blood. This case was discarded as not being a true angioma.

Ferrari, in 1891, reported a case in which a rose-red tumor "the size of a hazel-nut" was found beneath the left true cords. This was removed and excessive hemorrhage followed. The patient died from pneumonia. The growth was a telangiectatic angioma.

Schrötter, in 1891, found a "pea-sized" pedunculated varix on the left arytenoid epiglottic fold; it was removed, but a definite diagnosis was not made. Schrötter observed a patient who had a small nodule on the vocal cord, which was composed of a convolution of very small vessels but he could not make a histologic diagnosis.

Chiari,<sup>6</sup> in 1891, reported 15 cases of tumors of the cords, and 8 of these he called fibromas, because the septa between the spaces

were thicker than in cases of true lymphangioma, but Fein, in discussing them, declared his opinion that some of them resembled microscopically his case of lymphangioma.

Grant, in 1896, described a case of submucous hemorrhage of the vocal cord in a woman aged 24. He mentions recurring attacks of bleeding but on removal of the tumor there was practically no hemorrhage. No diagnosis was given. Chiari,<sup>7</sup> in discussing this case, says he does not think it is a true angioma.

Milligan, in 1905, showed a series of photomicrographs, one a hemangioma of the left cord, and another lymphangioma of the vocal cord. He did not give the case histories nor did he mention whose cases these were.

Symonds, in 1905, mentioned a patient with a true angioma of the larynx who had been seen by Mackenzie, Wolfenden, and Bond, but he did not state who had reported the case, and it was not, therefore, included as a new case.

Safranek, 1911, described a case of a woman aged 27. She had been hoarse since childhood. Both cords were thickened, and near the center of the left cord was a bright red, smooth, pedunculated tumor the size of a "pepper corn." The tumor was surrounded by small elastic vessels which on pressure gave the feeling of being well filled. Safranek called this a "penduculated angioma" or, possibly, a fibroma with change in the vessels.

TABLE 1.—HEMANGIOMAS

No.	Author	Sex	Age	Dura- tion of sym- ptoms	Structure involved	Number of tumors	Diagno- sis	Associated general pathology	Reported	Remarks	Size of tumor
1	Fauvel, I.....	...	53	1 yr.	Ant. commissure	1	Micro.	None mentioned	Cavernous hem- angioma	.....	Filbert
2	Fauvel, II.....	M	37	72 mos.	Lt. true cord	1	Micro.	None mentioned	Cavernous hem- angioma	.....	Pea
3	Heinze.....	M	38	Several years	(1) Rt. vent. fold (2) Same, behind	2	Clin.	None mentioned	Cavernous hem- angioma	.....	Pea Half a lentil
4	Mackenzie.....	.....	.....	.....	Rt. hyoid fossa	1	Clin.	None mentioned	Cavernous hem- angioma	Description of cases very brief	Blackberry
5	Mackenzie.....	.....	.....	.....	Rt. ventricular band	1	Clin.	None mentioned	Cavernous hem- angioma	.....	Blackberry
6	Elsberg.....	M	37	6 yrs.	Rt. true cord	1	Micro.	None mentioned	Cavernous hem- angioma	Considerable hem- orrhage on re- moval	Pea
7	Elsberg.....	M	28	5 yrs.	Rt. true cord	1	Micro.	None mentioned	Cavernous hem- angioma	.....	Third of length of right cord
8	Kidd.....	F	50	8 yrs.	Lt. true cord	1	Micro.	None mentioned	True angiomas	Bilateral and ped- unculated	Half of length of cord

Schwartz.....						1	Clin.				Wolfenden classi- fies it as true hemangioma
9											
10	Seiler.....					1	Clin.		Hemangioma		Called true an- gioma
11	Wolfenden.....	M	44	20 yrs.		2	Clin.		Hemangioma		Supposed to be Mackenzie's case
12	Brown	M	26	3 wks.		1	Clin.		Hemangioma		Rt. false cord size of raspberry. Other very small
13	Glasgow.....	M	20	5 mos.		1	Micro.		True hemangioma		Nothing done for patient
14	Loomis.....	F	62			2	Micro. autopsy		True hemangioma		Almost length of false cord
15	Bean.....	M	?			1	Clin.		Hemangioma		Pea
16	Bean.....	M	?			1	Clin.		Hemangioma		(1) Pea (2) Cherry
17	Solis-Cohen.....	?	?						Hemangioma		Nothing done ?
									Hemangioma		Removed with for- ceps
									Hemangioma		Mentions has had 2 cases in own practice. No data given
18	Solis-Cohen.....								Hemangioma		Described as blu- ish-black. Lo- cated most fre- quently on cords
											Vary from pea to mulberry



TABLE 1.—*Continued*

No.	Author	Sex	Age	Duration of symptoms	Structure involved	Number of tumors	Diagnosis	Associated general pathology	Reported	Remarks	Size of tumor
19	Chiari.....				Rt. true cord	1	Micro.	.....	True angioma	Bilroth diagnosed it microscopically as cavernous angioma. Chiari called it a varix.	1 mm. diameter
20	Jurasz.....	M			Lt. true cord	1	Clin.	.....	Hemangioma	.....	Larger than a lentil
21	Jurasz.....	M			Rt. true cord	1	Clin.	.....	Hemangioma	All treated with caustic punctures	Half as large as a lentil
22	Jurasz.....	F			Ant. half of rt. cord	1	Clin.	.....			
23	Brady.....	M	6		Subglottic and commissure	1	Clin.	.....	Angioma	.....	Cherry
24	Symonds.....	M		10 yrs.	Band rt. ventricle	1	Clin.	Syphilis	Angioma	Patient had lues ? 10 yrs. before exam.	?
25	Wingrave.....	M	43		Lt. true cord	1	Micro.	.....	True angioma	Reports 18 angiomas, only 1 true hemang.	?
26	Vitto-Massei.....		50	4 yrs.	Lt. pyriform sinus	1	Micro.	.....	Cavernous angioma	.....	Large
27	Navroiti.....	F	31	9 mos.	Lt. true cord	1	Clin.	.....	True angioma	.....	Extended beyond left cord
28	Blegvad.....	M	7	Few mos.	Lt. true cord	1	Micro.	.....	Angioma	.....	Millet seed

29	Safranek.....	F	51	6 mos.	Rt. arytenoid	1	Clin.				Smaller than ten cent piece
30	Pistre.....				Rt. true cord	1	Micro.		Cavernous angioma		
31	Thurber.....	M	31	3 yrs.	Rt. ventricle	1	Clin.		Angioma		
32	Ryerson.....	F	55		(1) Lt. true and false cords (2) Rt. arytenoid	2	Clin.		Angioma	Radium used successfully	(1) Raspberry (2) Smaller than raspberry
33	Loubert.....	?	?		Subglottic	1	Clin.		Angioma		
34	Phillips and Ruh..	M	9 mos.	4 mos.	Outer lateral wall extends from cords down to third tracheal ring	Diffuse	Micro.	Pneumonia, stenosis of larynx	Simple hemangiomas	Diagnosed at autopsy	Diffuse and flattened
35	Martuscelli and Porfida	M	32		Filled lumen of larynx	1	Micro.		Angioma with amyloid degeneration	Mentioned by New in article on amyloid tumors of larynx	Chestnut
36	Roux.....				Vocal cords					No data given except location of tumor	
37	Roux.....				Vocal cords					No data given except location of tumor	
38	Roux.....				Vocal cords					No data given except location of tumor	

## HEMANGIOMAS—Continued

No.	Author	Sex	Age	Dura- tion of sym- ptoms	Structure involved	Number of tumors	Diag- nosis	Associated general pathology	Reported	Remarks	Size of tumor
39	Roux.....	..	..	.....	Lt. arytenoid	..	.....	.....	.....	No data given ex- cept location of tumor	
40	Mayer.....	F	52	1 yr.	Lt. false cord al- most filling lu- men of glottis	1	Micro.	.....	Angioma	Removed by thy- rotomy and cau- tery. Found 27 cases recorded in- cluding his own	2. cm. by 1.5 cm.
41	Meyer.....	M	13	.....	Rt. vocal process and extended subglottically	1	Micro.	.....	Cavernous angi- oma	Reported at Ber- lin Laryngologi- cal Society, 1903	
42	Bioggi.....	M	42	2 yrs.	.....	2	Micro.	.....	Cavernous angi- oma		
43	Levbarg.....	M	10 wks.	Since birth	.....	1	Clin.	Hemangiomas, palate, neck. Paralysis lt. up- per extremity	Cavernous angi- oma	Intubation was done, x-ray treat- ment; symptoms improved	
44	McKinney.....	M	35	6 mos.	Pedunculated, at- tached subglottis to rt. cord	1	Micro.	Lues III, paralysis lt. area	Angioma	.....	Pea
45	New-Clark.....	F	9 mos.	6 mos.	Lt. subglottic re- gion	1	Clin.	.....	Cavernous angi- oma	.....	1.25 cm. by 1.875 cm.
46	New-Clark.....	F	45	.....	(1) Lt. arytenoid cartilage. (2) Ant. commissure	2	Micro.	T. B. rt. lobe. Dilatation arch of aorta	(1) Angiomatous/ fibroma. (2) Cavernous hemangioma	.....	(2) Pea
47	New-Clark.....	F	11 wks.	5 wks.	.....	1	Clin.	Cavernous angi- omas over face and scalp	Cavernous angi- oma	Larynx was not examined	

TABLE 2.—LYMPHANGIOMAS

No.	Author	Sex	Age	Dura- tion of symp- toms	Structure involved	Number of tumors	Diagno- sis	Associated general pathology	Reported	Remarks	Size of tumor
1	Koehler.....	M	40	.....	Lt. aryepiglottic fold	1	Micro.	.....	Lymphangioma	Five months after removal it re- curred and micro- showed sarcom- atous elements	Walnut
2	Fein.....	M	38	Several months	Subglottic rt. cord	1	Micro.	.....	Lymphangioma	Dark fluid escaped on removal	
3	Harmer.....	F	16	10 yrs.	Rt. aryepiglottic fold	1	Micro.	Similar condition at base of tongue	Lymphangioma	Seen in Chiari's Clinic	
4	Menzel.....			.....	.....	..	Micro.	.....	Lymphangioma	Complete micro. description is given. Case his- tory omitted	
5	Heindl.....	M	48	.....	Ant. third rt. cord	..	Micro.?	.....	Lymphangioma	Seems to be some doubt as to whether this is a true lymphangi- oma.	
6	Prokrofsky.....	F	55	.....	Lt. ventricular fold	..	Micro.	.....	Lymphangioma	.....	Hazelnut
7	Prokrofsky.....	M	?	.....	Rt. true cord	..	Micro.	.....			
8	Richardson.....	?	?	.....	Rt. false cord and aryepiglottic fold	..	Micro.	.....	Lymphangioma	Author states he has been unable to find a similar case reported	5 by 3 by 2.5 cm.

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## AN UNUSUAL MALIGNANT TUMOR OF THE PHARYNX\*

C. M. CLARK

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Malignancy of the upper air passages, according to the observations of men who have written on the subject, is closely associated with acute and chronic inflammatory conditions. Many patients who have had a so-called catarrhal affection for years, frequently exaggerated by acute infections of the mucosa, have usually been subjected to direct local treatment. It has often been our experience that the patient attributes his condition to some previous trouble, frequently remote but so conclusive that undoubtedly there must be a direct connection between the two.

In the upper respiratory tract, especially around the larynx, a secondary infection sometimes develops through the ulceration of an early malignant growth. This is often observed in cases of epithelioma, when the neck, either one or both sides, becomes involved by a low grade chronic infection, manifested by a slowly developing, hard external swelling, which takes on the characteristics of a phlegmon and breaks down or has to be drained.

Recently a patient has been under observation on Dr. New's service, whose condition differed in some respects from the usual picture seen in the upper air passages. After a careful search in the literature extending back over a period of ten years I have been unable to find the description of a similar case. It is reported herewith:

The patient (Case 259107), a farmer, aged 45, presented himself for examination Feb. 3, 1919, complaining of pain in the throat and difficulty in swallowing and talking. Two weeks before the patient had had a sudden attack of coughing and gagging followed immediately by hoarseness which lasted five days; then the speech began to improve but the coughing continued and the throat remained painful. After seven days his condition gradually became worse. At the time of examination he could swallow liquids only; he talked in a whisper.

\* Reprinted from *Laryngoscope*, 1919, xxix, 579-580.

The Wassermann test, the urine, blood, and x-rays of the chest, were negative. The left cervical region presented a large thickening which extended forward over the larynx with all the symptoms of an acute inflammatory swelling. By direct examination the pharynx appeared slightly injected; otherwise it was normal. The indirect examination showed the left side of the larynx and the hypopharynx to be swollen and edematous. The swelling extended evenly across the midline and partially involved the right side of the hypopharynx and the larynx. No ulcerations or areas simulating malignancy were found; the intrinsic structures of the larynx were not visible. The left arytenoid was swollen and only slightly movable, the right arytenoid was swollen but motion was not interfered with. Respiration was obstructed and tracheotomy seemed inevitable, but after the use of hot packs and inhalations for three days the breathing improved slightly and the swelling became localized over the right cervical region. Feb. 6, 1919, the phlegmon was drained and six ounces of pus were evacuated. The sinus was kept open for two weeks with iodoform gauze to allow healing from below and hot packs were applied externally to facilitate drainage. Feb. 10, 1919, the patient was again examined by the indirect method. The edema and swelling had subsided noticeably and a flat ulcerated area, three-fourths of an inch in diameter, was seen along the left lateral aspect of the hypopharynx and extending into the left pyriform fossa. Microscopic examination of the tissue showed squamous-cell epithelioma.

The examination and observation of this patient seemed to show that the malignant condition must have been present for several weeks or months without causing symptoms and that a secondary acute infection metastasized to the deeper structures through the early lesion on the surface epithelium. It may be that cases of this nature are more common than our experience leads us to believe since we do not see them during the intermediary stage when the malignant features are completely masked by those due to acute infections, but we see them during the early or late stages when malignant features predominate.

Without a definite and correct diagnosis in such cases, which can be obtained only by microscopic examination of the tissue, the patient will seldom be given the advantage of the most improved methods of treatment.



## AMYLOID TUMORS OF THE UPPER AIR PASSAGES\*

G. B. NEW

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Amyloid tumors of the upper air passages are rare. They occur as part of a general amyloidosis in which other organs of the body may be involved, or as a local condition. The upper air passages more frequently than any other part of the body are involved in a local amyloidosis. These tumors may be divided into three types: (1) Diffuse subepithelial infiltration; (2) tumor forming local amyloidosis; (3) amyloid degeneration of a pre-existing tumor.

Wichmann in his history of amyloid disease states that Portal was the first to call attention to the similarity to lard of the substance found in certain diseased livers, and carefully to note the etiologic findings. It was not, however, until Rokitansky had published clear descriptions of the condition observed microscopically and had differentiated amyloid and fatty livers, that amyloidosis was definitely recognized.

Burow and Neumann in 1873 were the first to recognize amyloid tumors in the larynx; these were found at necropsy. Seven years before Burow had removed fibroid tumors from the palate of this patient, who at that time refused operation for similar tumors in the larynx. The authors believe that amyloid degeneration had occurred in the fibroid tumors.

In 1875 Ziegler, at necropsy, found multiple amyloid tumors of the tongue and larynx and believed them to be of syphilitic origin (Fig. 361). Since then numerous articles and case reports on the subject have appeared in the foreign literature. Seckel, Reich, and Pognat have contributed recent articles of note. Hooper in 1891 and Eisenbrey in 1916 contributed the only two case reports in the American literature.

\* Reprinted from *Laryngoscope*, 1919, xxix, 327-341.

*Incidence.*—From a thorough review of the literature I have been able to collect but 42 cases of amyloid tumors of the upper air passages; the 4 cases I have observed in the Mayo Clinic make 46

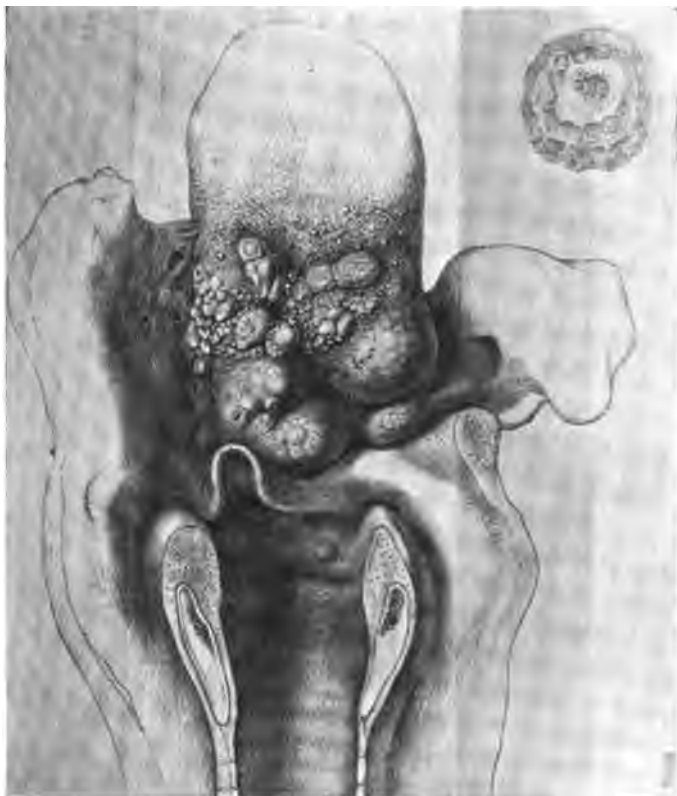


FIG. 361 Drawing (Ziegler's case).—Note the multiple tumors of the tongue and pharynx.

cases in all.\* The relative incidence of amyloid tumors of the larynx may be judged by the fact that only 4 cases have been found among 217 neoplasms of the larynx examined at the Mayo Clinic. Table 1, following Seckel's method of tabulating his 26 cases, shows the findings in the 42 cases reported in the literature and in my own 4 cases.

\* An additional case has been reported by Glinski, L. K.: (Amyloid tumor in the larynx.) *Prsegl. lek., Krakone*, 1914, liii, 417-421. I have been unable to translate this from the Polish.

*Age.*—The youngest patient with an amyloid tumor of the larynx was 20, the oldest 80. About half the patients were between 51 and 70; 10 patients were under 40.

Patients between 20 and 30 years. . . . .						2
"	"	31	"	40	"	8
"	"	41	"	50	"	5
"	"	51	"	60	"	11
"	"	61	"	70	"	11
"	"	71	"	80	"	4
Age not stated. . . . .						5
						<hr/> 46



FIG. 362 (170234).—Diffuse amyloid tumor, Type 1, of the entire circumference of the larynx and upper part of the trachea.

*Sex.*—Thirty-two of the 46 patients were males, 10 were females. In four instances the sex was not stated. In the cases reported males were affected three times as often as females; in my own cases all were females.

*Symptoms and duration of symptoms.*—The symptoms of the amyloid tumors of the upper respiratory tract vary with the location of the tumor. In many of the cases reported there were no local symptoms, but the condition was accidentally found at necropsy. When the larynx and the trachea are involved the symptoms are

such as accompany benign neoplasms of slow growth. In the cases reported by Gross and by Willimann, however, they were of short duration, five and six weeks respectively.

In the diffuse infiltrating type of tumor in which the larynx and trachea are affected, as in Case 1 and Case 2 of my group, early hoarseness and later (Case 1) dyspnea were noted. One patient (Case 4) came to the clinic for an abdominal complaint, but as at times she was slightly hoarse in the evening, she asked to have her

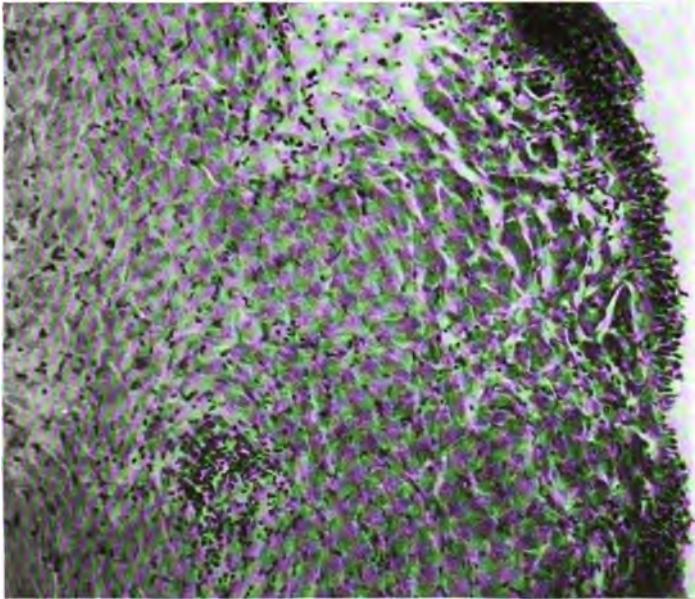


FIG. 363 (170234).—Photomicrograph. Subepithelial amyloid degeneration. Hematoxylin and eosin stain.  $\times 100$ .

throat examined. In Reich's case the patient had noted difficulty in breathing for fifteen years, but had been able to work. Burow's patient and my first patient required a tracheotomy for the laryngeal obstruction. Characteristic symptomatology of these tumors cannot be gathered from the case reports in the literature.

The exact duration of amyloidosis of the upper air passages is difficult to determine from the history of a case, as undoubtedly many patients have no symptoms for years. Some of the cases found at necropsy were not suspected during life. Balser's patient gave a history of nineteen years' duration, the longest history of any case reported. Reich's patient had symptoms for fifteen years.

*Location of tumors.*—Amyloid tumors of the upper air passages are most common in the larynx. They are found in the larynx three times as often as in the trachea, which comes next in the order of frequency. The larynx or the trachea was involved in 38 of the 46 cases, the larynx alone in 27, the trachea alone in 5, the trachea and larynx in 6, the tonsil in one, associated with the condition in the tongue, and the pharynx in one, associated with the condition in the larynx. In one patient (Glockner's) three organs were affected, the larynx, the trachea, and the bronchi.

#### ORGANS INVOLVED

Tongue . . . . .	9	Larynx. . . . .	33
Tonsil . . . . .	1	Trachea . . . . .	11
Pharynx . . . . .	1	Bronchi . . . . .	2



FIG. 364 (211230).—Uniform involvement of both vocal cords and subglottic region with the diffuse subepithelial type of amyloid degeneration.

*Clinical findings.*—The clinical findings of amyloid tumors of the upper respiratory tract are by no means uniform. While many of the cases present a picture that is seen in amyloid tumors only, others present one that is impossible to distinguish clinically from that of other benign neoplasms, from gumma, or from malignant growth, as in Willimann's case.

The diffuse subepithelial infiltration (Type 1) was seen in Case 1 and Case 2 of my group; the mesial margins of the true cords and the entire circumference of the subglottic region and upper part of the

trachea were rather uniformly thickened, causing a narrowing of the glottis and trachea. Balser's case also seems to be of this type, which is by far the less common type seen in the upper air passages.

Local amyloidosis of the upper air passages occurs most often in nodular form. Multiple or single nodules which may be pedunculated or sessile develop in the tumor, forming local amyloidosis (Type 2). Eleven cases in the literature were of the multiple type. The tumors occur in different sizes and shapes, but all tend toward the rounded or oval form. Case 4 of my group is interesting on account of the bilateral symmetrical tumors of the anterior part of the false cords.



FIG. 365 (234587).—Bilateral symmetrical amyloid tumors of the anterior part of the false cords.

Amyloid degeneration may develop in a pre-existing tumor (Type 3) such as a fibroid, as in Burow's and Neumann's case, or in an angioma, as in Martuscelli's and Porfidia's case. Seckel suggests a classification of such tumors similar to that of our Types 1, 2, and 3. In his case the tumors were found in varying sizes on the larynx and pharynx.

The surface of amyloid tumors is usually mammillated; the tumors are quite firm when touched with a probe: the mucous membranes are not ulcerated, and in most cases they are a waxy yellowish gray, although Pinaroli, Martuscelli, Massei, and Pacinotti report that the mucous membrane in their cases was red.

Willimann's case presented uniform swelling of the diseased side of the larynx, much the same as seen in gumma or carcinoma;

the possibility of these conditions had to be excluded in making the diagnosis. In 2 cases the local amyloid tumor of the larynx was associated with carcinoma (Courvoisier, and Beck and Scholz), but Beck and Scholz believe that the two tumors in their case were entirely distinct.

*Diagnosis.*—Although the clinical picture is fairly typical of amyloid tumor, the diagnosis must be made microscopically. This is well illustrated by a recent case of mine which showed a clinical picture very similar to that of Case 1 and Case 2. The patient gave a history of twelve years' gradual loss of voice and increasing dyspnea. There was no ulceration in the larynx. The condition was diagnosed clinically as a diffuse amyloid tumor of the larynx and trachea, but microscopically it proved to be epithelioma (mixed tumor type). In some cases, however, as in my Case 2, it is quite possible to make a clinical diagnosis which the pathologist corroborates.

*Associated general pathology.*—It is an accepted fact that general amyloidosis occurs following certain chronic diseases, such as osteomyelitis, tuberculosis, and syphilis. In these cases the abdominal organs are usually extensively involved. The cases collected are of local amyloidosis without general degenerative processes, but the condition may be due to chronic inflammation elsewhere in the body. In many of the cases in the literature a local tumor without mention of any associated general pathologic condition is reported; when the data are complete many cases show a general pathologic condition, which may be sufficient to account for the local degenerative process.

Seckel's, Hueter's, Kraus's, and Pacinotti's patients had tuberculosis. Only 2 patients were suspected of having syphilis, those of Ziegler and of Schrank. Two patients (Balser's and Saltykow's) had a bronchiectasis. Chronic emphysema was associated with 3 cases of amyloid tumor of the tongue, and with 3 of the larynx and trachea. Nephritis was found in both of Saltykow's cases. In only one of my 4 cases was there an associated pathologic condition, a chronic cholecystitis, for which operation was done.

*Pathology.*—Many of the writers who have reported amyloid tumors of the air passages believe that they should not be called tumors, as they are simply enlargements of the part, due to the deposit of the amyloid substance, without accompanying cellular growth. From a strictly pathologic standpoint this view is correct. The microscopic pathology of this condition depends on the type of tumor

present. In the diffuse, and in the tumor-forming type of local amyloidosis a subepithelial infiltration of the amyloid substance is noted. The blood vessels are especially affected. The mucosa and submucosa are elevated by the amyloid deposit which is seen in layers closely packed between connective tissue. In the cases of amyloid degeneration of a tumor, as, for example, of a fibroid or of an angioma, the characteristics of the original growth, as well as of the amyloid degeneration, may be found. The amyloid gives the characteristic staining reaction with iodine, and shows up distinctly with hematoxylin and eosin.

*Treatment.*—In many of the cases recorded in the literature the tumor appeared as a small nodule on the vocal cord and was readily removed perorally. In cases of localized tumors surgical removal, either by the endoscope or by thyrotomy, seems indicated. Uffenorde and Pognat removed the tumors from their patients by endoscopic methods. Reich reports the successful removal of an amyloid tumor of the trachea by external operation.

If the amyloidosis is diffuse and involves the entire circumference of the larynx and trachea the removal will probably result in the loss of voice and necessitate the permanent use of a tracheotomy tube because of secondary contractions. The procedure seems justified, however, if the disease is extending down the trachea, as in my Case 1.

Willmann reports a case in which an amyloid tumor of the larynx entirely disappeared after two x-ray treatments. The treatments were six weeks apart, the first time one "Sabouraud," and the second time one-half Sabouraud strong.

I have employed fulguration and radium with marked improvement in my cases, except in Case 1 in which a thyrotomy was done and the diffuse amyloid infiltration that involved the circumference of the larynx and trachea was removed. This was followed by treatment with radium.

#### REPORT OF CASES

Case 1 (170234).—Mrs. C. R., aged 56, was examined in the clinic Aug. 22, 1916. The patient had been hoarse for one year following an attack of the grippe and a severe cough, which she believed to be the onset of her trouble. Dyspnea, which was gradually increasing, was noted seven months before examination. A physician,



who had been consulted four months before, discovered a laryngeal growth. The patient had no trouble in swallowing, no cough, no expectoration, nor pain. She had lost 25 pounds in weight. The general examination was negative except for laryngeal findings. The Wassermann test, urine, sputum, and x-ray of the chest were negative. There was thickening of the entire circumference of the larynx at the level of the true cords, involving their mesial margins and extending down into the trachea (Fig. 362). A small finger-like process extended into the glottis from the anterior commissure. The mucous membrane was yellowish gray, the tissue was waxy. The cords were partially fixed. The patient could speak only in a whisper. Subepithelial amyloid degeneration was found in the tissue removed from the larynx for diagnosis (Fig. 363). Because the entire circumference of the larynx and trachea were involved, it was decided that a radical operation would cause tracheal and laryngeal stenosis. The patient was, therefore, treated with radium; the radical operation to be done later if necessary.

The first radium treatment was given Dec. 1, 1916; 100 mg. radium were dropped into the larynx and trachea after cocainization; eleven hours of treatment were given at different sittings. The patient went home and did not return to the clinic until Jan. 8, 1918. She stated that in September, 1917, it had been necessary to have a tracheotomy done for marked dyspnea. Radium was given outside the larynx. As the trouble was extending down into the trachea it was thought advisable to do an exploratory operation.

March 19, 1918, thyrotomy was performed (E. S. Judd). The hyoid bone was divided and the upper part of the trachea exposed. The mucous membrane of the upper part of the trachea and of the subglottic region involving the mesial margins of the cords was thickened and presented an irregular mammillated appearance. This thickened mucous membrane was removed by means of scissors; the wound was cauterized. Stenosis of the trachea and larynx developed during convalescence and despite attempts to keep these open the patient was obliged to continue wearing a tracheotomy tube. Radium treatment has been given from time to time; there has been no recurrence.

Case 2 (211230).—Mrs. C. C. T., aged 44, gave a history of loss of voice for three and one-fourth years. At the onset of the trouble

the patient had a severe cold, which lasted three weeks, with hoarseness. The hoarseness continued to grow worse and for the last two years she had been able to speak only in a whisper. She had no cough, no expectoration, nor dyspnea. She had gained 25 pounds in the last two years. The nose and throat examination was negative except for the laryngeal findings. The portion of the larynx above the true cord was normal. The mesial margins of the true cords and the entire circumference of the larynx at this level and in the subglottic region showed rather irregular and mammillated thickening that was of a yellowish gray, waxy color (Fig. 364). There was no ulceration. The general examination was negative except for fibroids of the uterus. The Wassermann test, x-ray of the chest, the sputum, and the blood count were negative.

Tissue removed for diagnosis showed subepithelial amyloid infiltration. Radium treatments were begun April 20, 1918; a 100 mg. tube for forty hours over the larynx, with one inch elevation, and 2 mm. of lead screening were used. A second treatment was begun Nov. 22, 1918; a 100 mg. tube for fifty hours was used. There was a marked improvement in the laryngeal condition and in the character of the voice. The patient can now make herself heard at some distance.

Case 3 (222018).—Mrs. J. D., aged 36, came to the clinic February 23, 1918, for hoarseness noticed seven years before. A physician had been consulted at that time, and the x-ray and medicine internally had been used. The patient's voice never became normal; she did not cough nor expectorate, but was slightly dyspneic on exertion. There was no loss of weight. The general examination was negative. The nose and throat examination was negative except for laryngeal findings. A sessile tumor, nodular and yellowish waxy, involved the left side of the larynx and the anterior commissure, and bulged to the midline of the glottis. There was no area of ulceration. The left cord could not be seen, but the right cord motion was not impaired. The tissue removed for diagnosis showed it to be an amyloid tumor. As the patient did not wish to have a radical operation done, as much as possible of the tumor was removed by indirect method, and the base was fulgurated. This procedure was repeated July 15, 1918. The patient was advised to have a thyrotomy with removal of the tumor, but she has not as yet returned to have this done.

TABLE 1

No.	Author	Publication	Sex	Age	Duration of symptoms	Location						Diagnosis			Associated general pathology	Remarks
						Tongue	Pharynx	Larynx	Trachea	Bronchi	Number of tumors	Clinical	Autopsy	Operative		
1	Burow and Neumann	Arch. f. klin. Chir., 1875.	M	50	10 yrs.			+			3	+	+			Three tumors diagnosed as fibroids removed and tracheotomy done 7 yrs. before death.
2	Ziegler	Virchow's Arch., 1875	M	67		+		+						+	Fatty degeneration of the heart	
3	Balser	Virchow's Arch., 1883	M	64	19 yrs.				+	+		+	+		Emphysema, pneumonia, bronchiectasia	
4	Massei I.	Arch. ital. di laringol., 1884-5	M	38				+			Multiple	+				
5	Massei II.	Arch. ital. di laringol., 1884-5	M	50				+			Multiple	+				
6	Kraus I.	Zschr. f. Heilk., 1885	M	36		+					1	+	+		Tuberculosis	
7	Kraus II.	Zschr. f. Heilk., 1886	M	?				+			1	+	+		Emphysema, pneumonia	
8	Hooper	Med. Rec., 1891	M	53	4 yrs.			+						+		
9	Schrank	Inaug.-Diss., 1892	F	35				+			1			+	Syphilis (?)	
10	Schmidt I.	Virchow's Arch., 1896	M	58		+					2	+	+		Bronchitis, emphysema	
11	Schmidt II.	Virchow's Arch., 1896	F	60		+					1	+	+		Emphysema	
12	Martuscelli I.	Arch. ital. di laringol., 1896						+			1			+		
13	Martuscelli II.	Arch. ital. di laringol., 1896						+			1			+		
14	Martuscelli III.	Arch. ital. di laringol., 1897	M	20	Mon.			+			1	+				
15	Schröter	Verh. d. deutsch. Gesellsch., 1899	F	57					+							
16	Mannase	Virchow's Arch., 1900	M	63				+			Multiple	+	+		Perforating duodenal ulcer	

[illegible]

TABLE 1.—Continued

No	Author	Publication	Sex	Age	Duration of symptoms	Location				Number of tumors	Diagnosis			Associated general pathology	Remarks
						Tongue	Tonsil	Pharynx	Larynx	Trachea	Bronchi	Clinical	Autopsy	Operative	
33	Reich.....	Beitr. z. klin. Chir., 1909	M	44	15 yrs.					+				+	Moderate emphysema
34	Beck and Scholz	Arch. f. Laryngol., 1909	M	63	2 yrs.					+				+	Epithelioma of the larynx.
35	Pinaroli.....	Arch. ital. di otol., 1910	M	40	1 yr.					+				+	
36	Lukesch.....	Wien. klin. Wchnschr., 1911	M	65						+			+		Died of heart failure.
37	Uffenortle.....	Monatschr. f. Ohrenh., 1911	M	64	wks.					+				+	
38	Seckel.....	Arch. f. Laryngol., 1912	M	62	6 mos			+	+						Miliary tuberculosis
	Chiari.....	Deutsch. med. Wchnschr., 1912													
39	Willmann.....	Arch. f. Laryngol., 1912	M	55	6 wks.				+						
40	Martuscelli and Porfida	Gior. inter. d. sc. med., 1914	M	32					+				+		Diagnosed as angiona and removed. Microscopically, it was a hemangioma which had undergone amyloid degeneration.
41	Eisenbrey.....	Proc. New York Path. Soc., 1916	F	66										+	Diagnosed as carcinoma and removed.
42	Pugnat.....	Rev. de Laryngol., 1918	M	52	7 mos.				+					+	
43	New I.....	170224	F	56	1 yr.				+	+				+	Nothing of note
44	New II.....	211230	F	44	3 1/4 yrs.				+	+			+	+	Fibroids of the uterus
45	New III.....	222018	F	36	7 yrs.				+				+	+	Nothing of note
46	New IV.....	234587	F	52	6 mos.				+				+	+	Chronic cholecystitis
	Glinaki.....	Pragel. lek. Krakone, 1914													

Case 4 (234587).—Mrs. M. W. W., aged 52, came to the clinic June 13, 1918, on account of abdominal trouble. Because of hoarseness occasionally evenings during the past five months the patient asked to have her throat examined. She was not dyspneic. The examination of the nose and throat was negative except for the laryngeal findings. The voice was slightly husky. There was a bilateral tumor of the anterior half of each false cord that was continuous with the rest of the cord (Fig. 365). The tumors almost approximated in the midline and obstructed the view of the true cords anteriorly. The mucous membrane was normal in color, but somewhat mammillated. The cords approximated normally posteriorly. The general examination showed nothing of note. The Wassermann test, x-ray of the chest, the blood count, and the sputum were negative. Amyloid infiltration was found in the tissue removed from both tumors. On account of their location it was thought best to fulgurate perorally. This was done four times by the indirect method, the first time June 26, 1918, and the last time April 30, 1919. The tumors have been much reduced in size and the patient's voice is almost normal.]

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## THE SURGICAL TREATMENT OF CYSTS OF THE THYROGLOSSAL TRACT\*

W. E. SISTRUNK

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Very early in fetal life the thyroid gland develops at the base of the tongue and, before the cartilage of the hyoid bone has formed, descends in the midline of the neck to its normal position. The epithelium lining this tract through which the thyroid descends normally disappears early in fetal life, although it occasionally fails to obliterate and in such instances isolated areas of thyroid tissue (aberrant thyroids) or cysts may develop along its course. It seems quite likely that the portion of the tract lying above the hyoid bone often retains its epithelium and patency and opens directly into the mouth through the foramen cecum near the base of the tongue. A persistence of this portion of the duct explains the development of cysts along this tract which do not appear in young children but are first noticed a number of years after birth. In such instances it is probable that any secretion which developed from the epithelium-lined tract emptied directly into the mouth through the foramen cecum and that at some time infection occurred in the duct and closed the opening into the foramen cecum. Any fluid accumulating in this duct after the opening in the foramen cecum has become blocked, most likely travels downward, following the tract made by the descending thyroid, and presents itself as a tumor in the midline of the neck near the hyoid bone.

In 86,000 consecutive patients examined in the Mayo Clinic only 31 thyroglossal cysts were found. Eighteen of these were in males and 13 in females. The cysts appeared at all ages from birth to fifty-three years, the majority being noted in patients between the ages of twenty and twenty-five years. In 25 of these patients the cyst was found in the midline of the neck, near the hyoid bone.

The diagnosis of such cysts is usually not difficult and is made by the finding of a rather firm, cystic tumor in the midline of the neck,

\* Reprinted from *Ann. Surg.*, 1920, lxxi, 121-123.

near the hyoid bone or the thyroid cartilage. When this is palpated the duct which runs from the cyst to the hyoid bone may usually be felt. If the cyst is left alone, it gradually enlarges and often is drained surgically. In other cases infection occurs within the cyst and an abscess forms which also is often opened and drained. In either case a sinus remains which discharges the fluid secreted by the epithelium lining the tract. In many of the patients whom we have examined fistulas have been present which had persisted for periods varying from six months to twenty-nine years.

The majority of operations for the cure of thyroglossal cysts are unsuccessful unless the epithelium-lined tract, running from the cyst to the foramen cecum, is completely removed. As a rule, the cyst and the portion of the tract lying below the hyoid may be dissected out without difficulty, but above this the tract is usually so small and friable that it is broken off easily and consequently is difficult to remove. We have learned, after having failed to cure certain patients in whom the duct was broken off between the hyoid bone and the foramen cecum, that better results are obtained when no attempt is made to isolate the duct above the hyoid bone. Instead of attempting this, the usual procedure, we remove with the duct the tissues surrounding it for a distance of about one-eighth of an inch on all sides, coring out, as it were, the tissues between the hyoid bone and the foramen cecum in a line, which the tract almost invariably follows, drawn at an angle of 45 degrees from the upper surface of the center of the hyoid bone in the midline of the neck, backward, and upward, toward the base of the tongue (Figs. 366 and 367).

The operation we usually perform is as follows: A transverse incision, about 2 inches in length, is made across the neck at about the level of the hyoid bone and the skin and platysma muscle are reflected. The cyst will be found lying beneath the raphé connecting the sterno-hyoid muscles. It is dissected free from the surrounding tissues up to the hyoid bone. At this point the tract usually passes through the hyoid bone, although it is sometimes found passing above or below it. We then separate the muscles attached to the center of the hyoid and remove a portion of the bone about one-fourth of an inch in length; next, without any attempt to isolate the duct, we core through the tissues at this point directly to the foramen cecum (Fig. 368), removing with the duct the tissues surrounding it for a distance of about one-eighth of an inch on every side. In order to do this, it is necessary to

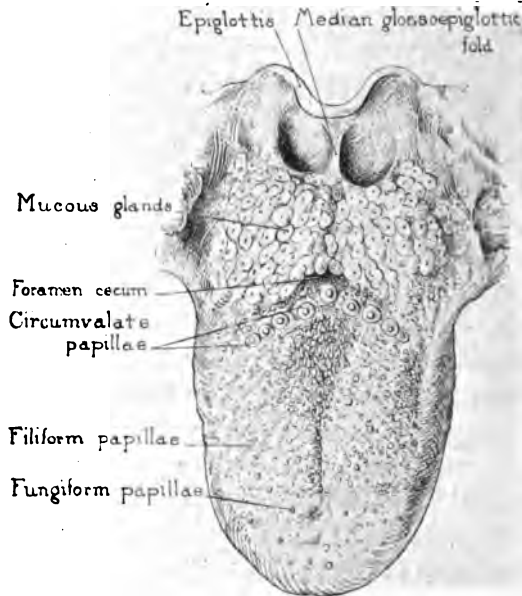


FIG. 366.—Anatomy of the dorsal surface of the tongue and the position of the foramen cecum.

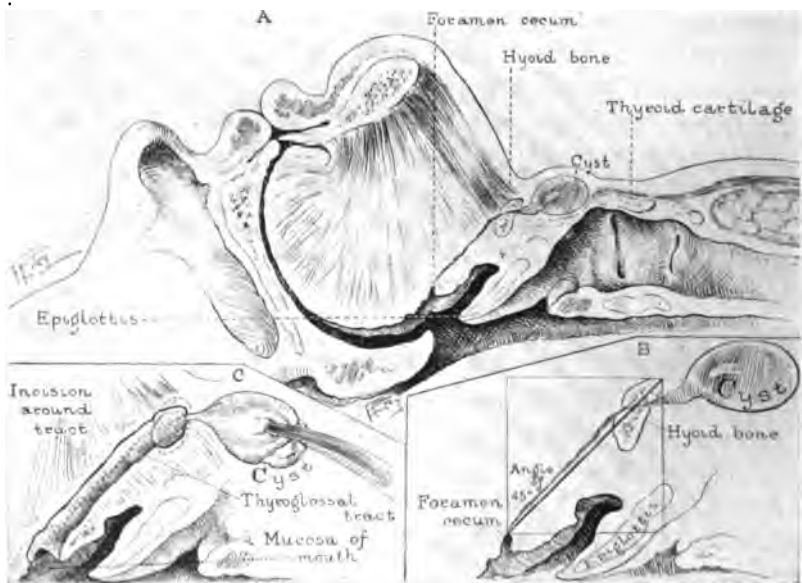


FIG. 367.—A. Sagittal section of the head giving the usual direction of the thyroglossal tract. The cyst is shown presenting between hyoid bone and thyroid cartilage. B. Dissection of duct to be made along an imaginary line drawn at an angle of  $45^\circ$  from the intersection of lines drawn horizontal and perpendicular to the middle of the anterior superior portion of the hyoid. C. The duct with muscles surrounding it being "cored out" along the line shown.

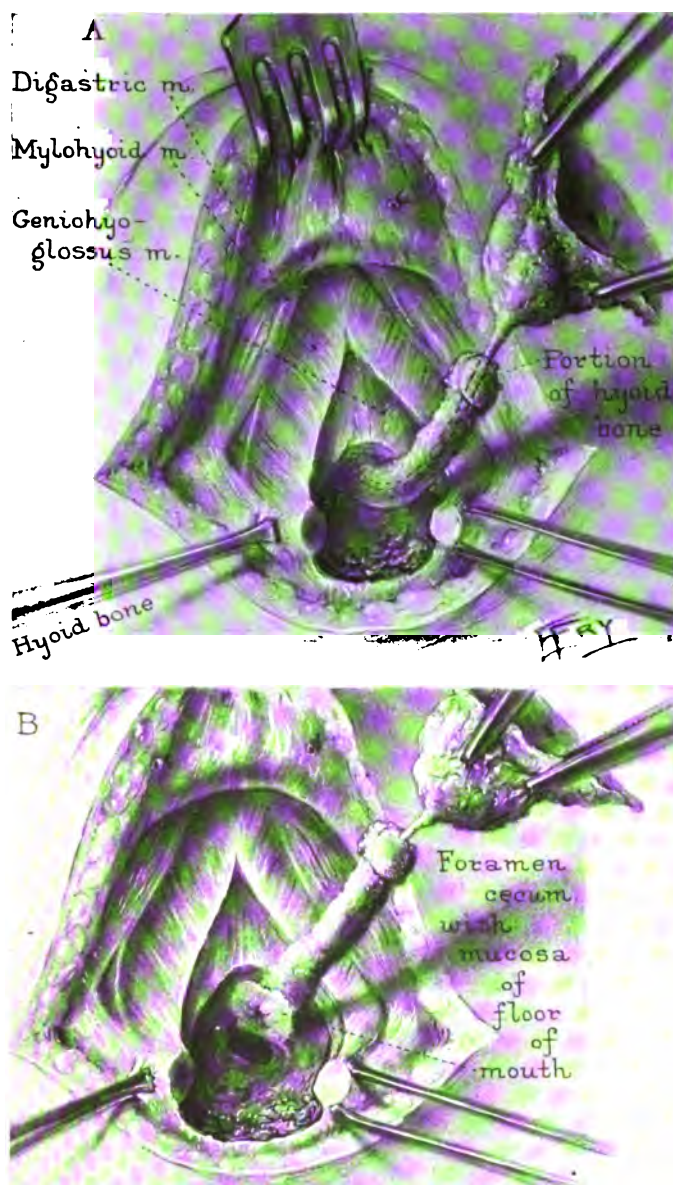


FIG. 368.—Steps of the operation. A. A segment of hyoid has been removed and the duct with the surrounding tissues is being dissected out. B. The dissection has been extended through the tongue; the foramen cecum may be seen.

know very accurately the direction that must be followed in order to reach the foramen cecum. This line corresponds to one drawn at an angle of 45 degrees backward and upward through the intersection of lines drawn horizontal and perpendicular to the superior central portion of the hyoid bone. The dissection removes with the duct, a portion of the hyoid bone, a portion of the raphé joining the mylohyoid muscles, a portion of each geniohyoglossus muscle, and the foramen cecum. The opening into the mouth is closed and several sutures are used to draw the geniohyoglossus muscles together; the tissues surrounding the cut ends of the hyoid bone are then brought together with chromic catgut sutures in such a manner as to approximate the edges of the bone. A small rubber tissue drain is introduced down to this point and the skin closed around it. It is probably best to inject sinuses with some dye such as methylene blue in order that any lateral branches, and these are occasionally found, which may be present between the hyoid bone and the foramen cecum may be recognized and removed. We have never seen ill effects follow the removal of a portion of the hyoid bone, nor have we ever seen infection of a serious character follow the opening made into the mouth.

## STUDIES IN INFLUENZA AND PNEUMONIA

### II. The Experimental Production of Symptoms and Lesions Simulating Those of Influenza with Streptococci Isolated During the present Pandemic\*

E. C. ROSENOW

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During a study made some years ago<sup>3</sup> on the influence of environment on the pneumococcus-streptococcus group of microorganisms, I noted marked changes in morphology, growth characteristics, infecting powers, and immunologic reactions. Many of these changes appeared to be true mutations. Observations I have made since then, particularly during this epidemic, corroborate those findings and suggest the possibility that the present pandemic may be the result of infection by mutation forms of this group of microorganisms. In studying the infecting power, and other properties of streptococci when they are first isolated from tissues and foci of infection in various diseases including poliomyelitis, certain strains of streptococci which produce green discoloration on blood agar and which have peculiar infecting powers, specific immunologic properties and etiologic relationship have been found. In view of these facts, which are regarded as fundamental, it was thought possible that the peculiar clinical and pathologic picture of influenza, its accompanying pneumonia, and other lesions might be due to bacteria having peculiar infecting powers and other specific properties. The presence of a pandemic strain among the varieties of pneumococci and streptococci isolated by many observers was considered possible.

The somewhat peculiar green-producing streptococcus, described in a previous paper,<sup>4</sup> has now been isolated quite constantly from a large series of cases of influenza. In making cultures from the blood, from the lung exudate, and from peribronchial lymph glands in patients who died from acute pulmonary edema and pneumonia, we were struck

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by the fact that cultures in the former were often sterile or contained few colonies and that the bacteria, particularly green-producing streptococci, were few in number in the latter as compared, for example, with those found in lobar pneumonia. Following intraperitoneal injections in guinea pigs of the sputum and cultures, invasion by this organism was found in most instances, but, as in persons with influenza, the number of organisms in the blood was strikingly small



FIG. 369.—Lung of Guinea-Pig 761, injected intraperitoneally, showing hemorrhage, bronchopneumonia and emphysema. Total volume 12 c.c.

and far less than that found in animals dead from intraperitoneal injections of type pneumococci. A special mechanism for the cause of death was thus indicated. In the animals it was found that the organism, when injected intraperitoneally or intravenously, tended to localize in the lung and to produce hemorrhages and bronchopneumonia, associated with a varying degree of emphysema (Fig. 369). This was not noted in animals dead from intraperitoneal injections of type pneumococci. The average volume of the lungs, the total displacement of water of guinea pigs weighing about 350 gm., was found

to be as follows: normal guinea pigs killed with chloorform, 5.2 c.c.; guinea pigs dead from intraperitoneal injections of type pneumococci, 6.7 c.c.; and guinea pigs dead from intraperitoneal injection of sputum and green-producing streptococci from influenza, 12 c.c. Since localization tended to be in the lung it was thought that direct application of the organism to the respiratory tract might afford better opportunity to study the peculiar infecting power of the bacteria found during this pandemic.

A simple method for intrabronchial injections of guinea pigs was devised similar to that used in dogs by Lamar and Meltzer and in rabbits by Winternitz and Hirschfelder. Discarded ureteral catheter cut at an angle of 45 degrees with the margins rounded are used to make the injections. The guinea pig is wrapped in a towel, the head held in place by the handles of an inverted artery forceps. The mouth is held open by spring wire retractors and the tongue is depressed by a suitable small instrument. Under a strong reflected light, properly shaded, the catheter is inserted into the larynx with a quick stroke before the contraction of the muscles of the epiglottis can divert the tube into the esophagus. The animal's sharp, quick cough and total inability to use its voice, and the sensation of the catheter's passing the tracheal rings, indicate that it has entered the trachea. The injections, varying from 0.1 c.c. to 2 c.c. in amount, are made slowly through the catheter with a syringe and needle.

By this method numerous experiments have been done with various strains of bacteria, including pneumococci, green-producing streptococci, hemolytic streptococci, staphylococci, and influenza bacilli from persons with influenza as well as those from normal persons and other sources. The details of these experiments are reserved for subsequent reports; the purpose of this paper is to record a brief summary of the principal results obtained with strains of the green-producing streptococci and pneumococci belonging to Group IV from cases of influenza. By intrabronchial injection of these organisms a picture simulating influenza and pneumonia has been produced. Numerous animals have succumbed to acute pulmonary edema, to bronchopneumonia, to pneumonia involving whole lobes, and to acute hemorrhagic exudation in the pleura and pericardium together with marked or slight lung involvement.

The lungs of these animals, as in persons with influenza, were often voluminous. Many animals showed acute symptoms resembling





FIG. 370.—Lung of Guinea Pig 851, injected intratracheally, showing coalescing bronchopneumonia of enlarged right lower lobe. Total volume 18 c.c.

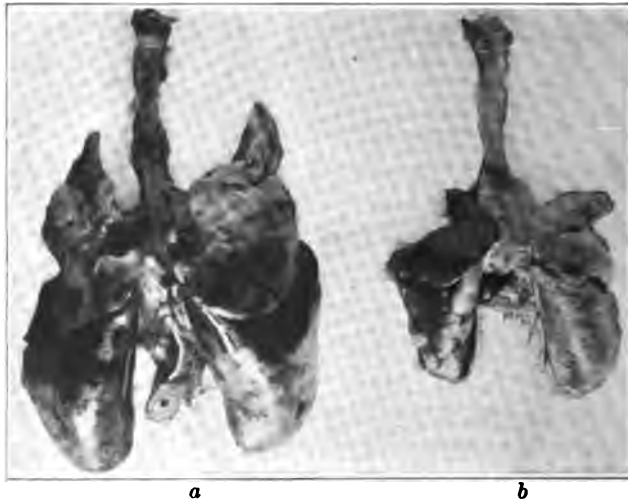


FIG. 371.—*a*, Lung of Guinea Pig 968, injected intratracheally, showing marked hemorrhagic edema and emphysema. Total volume, 22 c.c. *b*, Lung of guinea-pig of same weight dead from spontaneous pneumonia. Total volume 6.5 c.c.

anaphylactic shock and typical bronchial spasm a few minutes after intratracheal injection. The type of respiration in those that lived twenty-four hours or longer was often very different from that in the animals having respiratory embarrassment from extensive consolidation of the lung following injection of pneumococci from lobar pneumonia, or of mass cultures from throats of normal persons. In the former, the chest was often in almost complete expansion, the animals were irritable and restless, expiration was prolonged and difficult, and breathing was accomplished chiefly with the diaphragm. Injections of epinephrin and atropin in large doses often relieved the respiratory

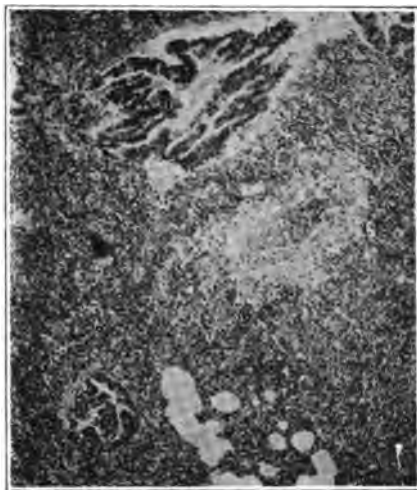


FIG. 372.—Section of lung shown in Figure 371 a, showing marked dilatation of alveoli, extreme contraction of bronchi, interstitial and alveolar hemorrhage, and infiltration. Hematoxylin and eosin.  $\times 70$ .

embarrassment. In the latter group of animals the respiration was normal in character, excursions of the chest were free and easy, and the animals were quiet, but the rate was often much increased, depending on the amount of consolidation. Injections of epinephrin and atropin were without effect. The lungs in the first group were often extremely emphysematous and contained much hemorrhagic edematous fluid (Fig. 370). The massive bronchopneumonia was the rule in the animals that died late (Fig. 371). The rupture of alveoli, manifested as subpleural blebs, has been noted in animals showing extreme emphysema and hemorrhage. In a number, air was found in the mediastinal tissues, and several showed subcutaneous

emphysema about the thorax. Sections of the lungs showed extremely narrow lumina of bronchi often filled with exudate. The mucous membrane appeared in great folds and the cartilages in the wall of the larger bronchi were often distorted as a result of the extreme spasm of the bronchial muscles (Fig. 372). The marked constriction of bronchi must have occurred before death and was not due to the fixation in 10 per cent formaldehyd solution, since the total volume of lungs after fixation in formaldehyd solution (Kaiserling's solution) was found to be only about one-sixth less than that of the fresh lung. This picture is identical to that of the anaphylactic lung obtained by the usual methods, except that marked edema and hemorrhage occurred in the mucous membrane of the trachea and bronchi and in the interstitial tissue and the alveoli. The lungs of animals injected with type pneumococci, or with mass cultures from influenza and from normal persons, were not much larger than normal. The mucous membrane of the trachea and bronchi appeared normal. There was little hemorrhagic edema, but a variable amount of consolidation occurred, usually of the lobar type. The bronchi were not constricted and the dilatation of alveoli was absent. In addition to the picture in the lung, many of the animals aborted and many showed localization in the uterus. The picture of influenza was simulated in still other ways. There was delayed coagulation of the blood obtained from the heart and lung exudate in the animals, as in persons dead from influenza. Leukopenia usually occurred following injection of the strains. Leukocyte counts were made in 195 animals, following injections of numerous strains and their filtrates. Eighty-eight of these showed marked leukopenia, forty-one moderate leukopeia, thirty no change, thirty marked increase, and thirteen slight increase in leukocytes. The strains from patients showing marked leukopenia produced, usually, leukopenia in animals, while those from patients with leukocytosis usually produced leukocytosis in animals. Many animals (Table 1) showed leukopenia for a day or two; they appeared sick or prostrated; and, as recovery ensued, the leukocyte count increased. A persistent leukopenia was the rule in the animals that died.

In Table 1 are given the leukocyte counts in a series of animals following the injection of a number of strains, together with controls injected with type pneumococci. All but one of nine animals injected with Strain 2800 showed a marked or moderate leukopenia, while

TABLE 1.—THE LEUKOCYTE COUNT FOLLOWING INJECTION OF GREEN-PRODUCING STREPTOCOCCI FROM INFLUENZA

No.	Inoculation		Leukocyte count				Duration of experiment in days	Results
			Before injection	Hours after injection		After death		
	Dose in c.c. of dextrose broth culture	Strain and place of isolation	Place of injection	24	48	72		
P. 959	0.1	2,800 sputum	Trachea	16,400	6,200	19,000	14,400	Recovery
P. 961	1.5	2,800 throat	Subcutaneous tissue	10,400	1,600	1,400	12,800	Death: subcutaneous cellulitis
P. 955	1.5	2,800 throat	Trachea	16,000	21,000	17,000	19,400	Recovery
P. 964	1.5	2,800* throat	Trachea	15,000	3,100	.....	3,100	Death; hemorrhagic edema and emphysema of lung
P. 969	2.0	2,800* throat	Vein	12,000	4,200	.....	4,400	Death; hemorrhagic edema and emphysema of lung
P. 981	1.5	2,800.2 blood	Trachea	8,000	2,000	6,200	12,000	Recovery
P. 995	1.5	2,800.2 blood	Trachea	9,600	6,200	14,000	.....	Recovery
P. 1043	2.0	2,800.2* blood	Trachea	10,800	2,000	.....	4,400	Recovery
P. 1058	2.0	2,800.4 blood	Trachea	12,000	6,600	5,000	8,000	Death; hemorrhagic edema and emphysema of lung
P. 990	1.0	2,799* sputum	Trachea	7,400	2,200	2,500	.....	Death; bronchopneumonia
P. 952	1.5	2,795.3 sputum	Trachea	16,200	.....	28,000	17,000	Death; bronchopneumonia and hemorrhagic edema
P. 1004	1.5	2,839 throat	Trachea	13,000	.....	2,600	.....	Death; hemorrhagic edema and emphysema
P. 1019	1.5	2,839 throat	Trachea	22,400	5,400	.....	5,400	Death; hemorrhagic edema and emphysema
P. 1174	1.5	2,981.2 stool	Trachea	18,000	6,800	9,400	9,400	Chloroformed; lobar pneumonia
P. 1023	1.5	Pneumococcus III	Trachea	6,600	4,400	7,800	.....	Recovery
P. 1025	1.5	Pneumococcus III	Trachea	6,800	6,800	6,800	.....	Recovery
P. 1026	1.5	Pneumococcus II	Trachea	14,400	5,400	9,000	.....	Recovery
P. 1027	1.5	Pneumococcus II	Trachea	16,800	16,600	15,400	.....	Recovery
P. 1031	1.5	Pneumococcus IV	Trachea	13,200	18,000	17,500	17,500	Death; lobar pneumonia

\* The figure to the right and above the figures indicating the strain designates the animal passage; the one following the period, the subculture.

one showed slight leukocytosis. This difference in the behavior of an occasional animal was noted with other strains. The results as shown in Table 1 represent in a general way those obtained throughout these experiments. In some instances the cultures and their filtrates became so toxic that very small doses sufficed to cause hemorrhagic edematous frothy fluid to exude from the nose and mouth before death, and marked emphysema and hemorrhagic edema of the lung were found after death. One filtrate was so toxic that the instillation of 0.3 c.c into the nostrils of a guinea pig caused death in forty minutes from hemorrhagic edema and emphysema of the lung.

The freshly isolated strains from influenza and its accompanying lesions have been found to produce relatively large amounts of "anaphylatoxin" both in vitro and in vivo. The idea that the virulence of these bacteria may depend in part on their ability to produce "anaphylatoxin" is in accord with my previous findings<sup>2</sup> that virulent pneumococci and their filtrates produce a larger amount of this toxic substance than avirulent pneumococci. The picture in animals is clearly that of an anaphylactic intoxication, and suggests that the symptoms and lesions in man as recorded by numerous observers may likewise be due to this cause in which sensitization of the host to the bacterial proteins may or may not play a part. Findings as follows indicate this mechanism: (1) the delay in the coagulation time of the blood, leukopenia, and cyanosis; (2) the marked tendency to develop acute pulmonary edema with a distended lung and relatively immobile expanded chest, and extreme respiratory effort; (3) the voluminous lung as found at necropsy; (4) the occurrence of the rupture of alveoli and consequent subcutaneous emphysema (bronchial spasm); (5) the frequency of abortion (contraction of unstriated muscle) and other uterine disturbances.

From this study it is clear that among the green-producing streptococci isolated by many observers in influenza and the accompanying pneumonia, a strain or strains occur which possess marked and peculiar virulence. By intratracheal injection of these strains the picture of influenza has been closely simulated.

#### PROTOCOLS ILLUSTRATIVE OF SOME OF THE RESULTS OBTAINED

PROTOCOL 1.—Guinea Pig 761, weighing 350 gm., was injected intraperitoneally, Nov. 26, 1918, with 3 c.c. of the dextrose-brain-broth culture from a single colony of the green-producing streptococcus

isolated on blood agar plates from the sputum of a typical case (Strain 2611) of influenza. November 27 the animal appeared quite well; November 28 it appeared sick, respirations had increased. November 29 it was found dead. Serofibrinous peritonitis and moderate emphysema of the lungs, a total volume of the lungs of 12 c.c., localized hemorrhagic edema and bronchopneumonia of the right apical, cardiac, and diaphragmatic lobes were found. The lung was edematous on the cut surface, and the edematous areas were surrounded by marked emphysema (Fig. 369). The pleura was normal. November 30, blood agar cultures of the blood revealed a moderate number of green-producing streptococci and a few staphylococci; those of the lungs showed a large number of green-producing streptococci and a few staphylococci, while blood agar cultures of the peritoneal exudate revealed countless numbers of green-producing streptococci and many staphylococci.

PROTOCOL 2.—Guinea Pig 851, weighing 500 gm., was injected intratracheally, Dec. 28, 1918, with 0.5 c.c. of the dextrose-brain-broth culture of a green-producing streptococcus from the sputum of a case of typical influenza (Strain 2749) after one animal passage. Jan. 3, 1919, the animal died. Marked cloudy swelling of the myocardium, distention of the right ventricle, hemorrhages in the adventitia of the pulmonary artery, voluminous lungs weighing 20 gm., with a total volume of 18 c.c., and marked hyperemia of the mucous membrane of the trachea and bronchi were found. The right diaphragmatic lobe was almost completely consolidated. The consolidation was clearly lobular in character, but numerous similar areas were completely coalesced. The left pleura was normal and the right was covered with a thick layer of adherent fibrin, particularly opposite the gray areas of consolidation (Fig. 370). There were no areas of softening; but a number of circumscribed areas of hemorrhage and edema in the emphysematous lobes were noted. Jan. 4, 1919, blood agar plate cultures of the blood showed a few colonies of the green-producing streptococcus; the pleural exudate, the pneumonic lung, the kidneys, and the mucous membrane of the nose showed countless numbers, while the edema fluid from the circumscribed areas in the emphysematous lung and the adrenals showed a few.

PROTOCOL 3.—Guinea Pig, 968, weighing 380 gm., was injected intratracheally Jan. 14, 1919, at 3:30 p. m., with 2 c.c. of the dextrose broth culture of the hemorrhagic vaginal discharge from a fatal case

(Strain 2800) of influenza. Blood agar plates of the culture injected showed countless numbers of green-producing streptococci and a moderate number of colon bacilli. At 7:30 p. m., the respiration was difficult and greatly increased. The animal was restless and irritable and coughed at intervals. At 7:40 p. m., the condition was worse; respirations were extremely rapid and labored, and a bloody fluid was noted about the nostrils. At 7:42 p. m., the animal had a violent attack of bronchial spasm, in which it threw itself about in the effort to breathe. It bled profusely from the nose and mouth, and died three minutes later. The lungs were heavy and enormously distended; their total volume was 22 c.c. (Fig. 371a). Numerous large and small hemorrhages were found throughout all the lobes. The alveoli, in places, appeared at the rupturing point. There was a small amount of bloody fluid in the pleural cavities. A large amount of bloody frothy fluid escaped from the larynx, and the nostrils were filled with similar material. The cut surface of the lung was extremely moist, dark red, and a large amount of hemorrhagic frothy fluid escaped. There were two small hemorrhagic fetal masses, one in the vagina and the other at the bifurcation of the uterus. The uterine horns were hyperemic. The placental mass surrounding the fetuses was hemorrhagic. A number of small hemorrhages were found in the mucous membrane surrounding the point of placental attachment. The amniotic fluid was clear and smears showed no bacteria.

January 16 the blood and mucus from both horns of the uterus were sterile. The lungs and kidneys showed a large number of green-producing streptococci and colon bacilli; the pleura showed colon bacilli, and the adrenal, spleen, and liver showed a few colonies of colon bacilli.

Sections of the lungs showed a striking picture of marked contraction of the bronchi, extreme dilatation of the smaller vessels, interstitial hemorrhage, and cellular infiltration alternated with areas showing marked dilatation of alveoli. The dilated alveoli were often distended with edema fluid, blood corpuscles, and leukocytes, or they were empty (Fig. 372). In the denser areas of hemorrhage and infiltration, the outline of the walls of the alveoli were wholly lost from edema and infiltration of interstitial tissue. The denser areas of infiltration were situated around the bronchi. A large number of gram-staining diplococci and a few bacilli were found in the infiltrated areas, both within the alveoli and the interstitial tissues.<sup>4</sup>

### III. The Occurrence of a Pandemic Strain of Streptococcus During the Pandemic of Influenza

The uniformity of symptoms in typical influenza suggests that the cause is a single bacterium having pandemic characteristics. The uniformity of the isolation of the somewhat peculiar green-producing streptococcus, previously described,<sup>4</sup> early in influenza and in the accompanying pneumonia, and the regularity of the invasion by this organism following the injection in guinea pigs and mice, indicated early in the work that a pandemic strain might be found among this

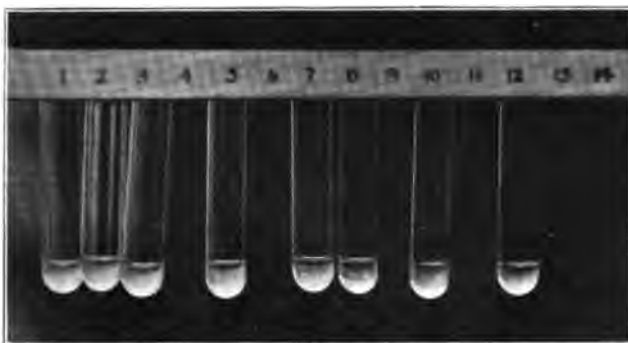


FIG. 373.—Photograph of experiment showing specific agglutination of streptococcus (Strain 3276) from influenza. Dilutions of serums 1–20. Tubes 1, 2, and 3 contain pneumococcus Types I, II, and III serums; Tube 5 contains hemolytic streptococcus serum, Horse 9; Tubes 7 and 8 contain the monovalent serum following the injection of one strain of green-producing streptococcus from influenza, the former from a bleeding made March 3, the latter from a bleeding made May 4. Note the greater agglutination in the latter serum, Tube 8; Tube 10 contains normal horse serum; Tube 12, salt solution.

group of streptococci. The experiments following intratracheal injection, in which the picture of this disease is closely simulated, further indicate this possibility, and immunologic experiments were therefore instituted. I wish briefly to record here the main results obtained.

The serum of convalescent patients has been found to agglutinate specifically some of the more sensitive strains. The increase in agglutinins has been noted as early as the third day of typical influenzal attacks. The serum of cases that occurred early in the epidemic is found to agglutinate strains isolated then and kept in 50 per cent glycerol as well as those isolated now, and vice versa. The results given in Table 2 suffice to illustrate those obtained in a large series of



cases. The amount of agglutination with the different strains varies greatly and some strains are not agglutinated at all.

A monovalent immune serum has been prepared in a horse with one of these strains isolated from the blood in a typical fatal case. The horse has been injected with increasing amounts, first with the dead bacteria and later with the living. The serum has developed marked agglutinating power (Fig. 373) over these strains, agglutination occurring in dilutions up to 1:1,000 and 1:10,000.

TABLE 2.—AGGLUTINATION EXPERIMENTS WITH HUMAN SERUMS

Serums from Influenza (Dilutions 1:10)	Day of disease	Strains from Influenza						
		3271 <sup>2</sup> . 3 Sputum	3296 <sup>2</sup> . 2 Sputum	3331 Sputum	3333. 2 Sputum	3333. 2 Throat	3334. 2 Sputum	Control Strain 3323 3
3074 (normal).....	..	0	++	+	++	+	0	0
3075 (normal).....	..	0	++	0	0	+	+	0
3076 (normal).....	..	0	++	0	0	0	0	0
3282.....	..	++	++++	++	++	+++	++	0
3283.....	13	++	+++	++	+	+++	+	0
3331.....	6	++	+++	+	+++	+++	++	0
3332.....	5	++	+	+++	+	+++	++	+
3334.....	5	+++	+++	++	++	++	++	0
3338.....	7	++	++++	++	+	++	0	0
3339.....	2	++	++++	++	++	++	++	0
3348.....	4	+++	+++	++	+++	++	+	0
3348.....	10	++	++++	+++	+++	++	++	0
3349.....	3	++	+++	+	+++	++	++	0
3349.....	9	++	+++	+++	+++	+++	0	0
NaCl.....	....	0	0	0	0	0	0	0

The agglutinating power of various immune horse serums, as indicated in the tables, has been tested against numerous strains isolated from the sputum, throat, blood, and lung exudate. The well known methods for determining types of pneumococci, with minor modifications, were used. These included the animal inoculation method as worked out by Cole and the dextrose-blood-broth method as worked out by Avery. The various serums indicated in Table 3, were diluted 1:10 and equal amounts of this and the broth culture or suspension (0.2 c.c.) were placed in each tube and mixed, incubated one hour, placed in the ice chest over night, and then readings were taken. This dilution was found, after a series of titrations, to be best suited for routine purposes. Specific agglutinations with the monovalent serum as indicated in Table 4 have thus far been obtained in 65 of a total of 98 cases studied. Some of these strains, just as has been found to be the case with the streptococcus from poliomyelitis, lose their specific character promptly on cultivation

while others remain susceptible to specific agglutination months after isolation. This was anticipated in the beginning of the work, and dense suspensions of the freshly isolated strains were placed in 50 per cent glycerol. This method was proved efficacious in studying the specific properties of the poliomyelitis strains, and has been found equally useful in this study. Many strains isolated in the beginning of the epidemic are agglutinated specifically by this serum prepared with a single strain isolated early this year (January, 1919), just as are the strains from typical influenza isolated since then. The cases studied came from widely separated communities. Most of the negative agglutinations occurred when the cultures were made during convalescence. The results in some typical cases, however, suggest the possibility of subgroups. The specific strain, according to this test, has been isolated from the sputum as early as the first day of influenza, from the sputum in the accompanying pneumonia, and from the blood and lung exudate after death. It tends to disappear promptly during convalescence and is rarely found in normal throats. Strains of green-producing streptococci from a wide range of sources are rarely agglutinated by this serum. In studying the agglutinating power of various immune serums over strains from the sputum daily or on alternate days throughout the disease, it has been found that the strains are agglutinated specifically by this serum throughout the course in typical cases in which the patients recover without developing pneumonia or in which the pneumonia is of short duration. This is not usually true, however, of patients with protracted or recurring pneumonia, especially those who die (Strain 3276, Table 3). In these there may be a shifting of agglutination to pneumococcus serums, Types II or III, to hemolytic streptococcus serum, or, more often, they may not be agglutinated by any of the serums. Most of the specific strains, according to this test, do not ferment inulin and are not bile-soluble.

The results obtained in this series of experiments are illustrated, in the main, in Table 3. It will be noted that the primary cultures (Strains 3208, 3297, 3301, 3302, 3276) and the peritoneal washings from mice (Strains 3225,<sup>2</sup> 3226,<sup>2</sup> 2327,<sup>2</sup> 3231<sup>2</sup>) were agglutinated specifically by this serum (Horse 15) in every instance as were the cultures from single colonies after animal passage (Strains 3208<sup>2,2</sup>, 3276<sup>2,2</sup>). The result in the third column (Strain 3208.2) shows that it is not always possible to fish the specific strain when the sputum or other material is plated directly.

TABLE 3.—AGGLUTINATION OF STREPTOCOCCI FROM INFLUENZA BY IMMUNE HORSE SERUMS

Immune serums (dilution 1:20)	Strains from												Miscellaneous sources											
	Influenza												Pneumonia											
3201.2	3208	3208.2	3208.2*	3225*	3226*	3227*	3231*	3271	3297	3301	3302	3276 3/29	3276* 3/29	3276.2 3/29	3276 3/31	4/3	3295 Lobar pneumonia	3342 Lobar pneumonia	3270 Bronchitis	2698 Pneumonia	2684 2 Lobar pneumonia	Pneumococcus I pneumonia	Pneumonia in guinea pig	
Pneumococcus I.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pneumococcus II.....	0	0	0	0	0	0	0	0	0	2+	+	0	0	0	0	2+	0	0	0	0	0	3+	0	0
Pneumococcus III.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0
Streptococcus (hemolytic from cellulitis) Horse 9.....	2+	+	3+	2+	3+	2+	2+	2+	0	0	0	2+	+	2+	+	0	0	0	3+	3+	0	0	0	0
Streptococcus (nonhemolytic from influenza) Horse 15.....	3+	0	4+	3+	4+	3+	3+	3+	3+	3+	3+	3+	3+	3+	+	0	0	0	0	2+	2+	0	0	0
Normal horse.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NaCl solution.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

\* The figures to the right and above the figures indicating the strain indicate the animal passage, those to the right of the period indicate the culture generation.

Many strains of the green-producing streptococcus from influenza have acquired hemolytic power in my hands and resemble closely the hemolytic streptococci isolated from some of the cases, especially after death. The close relationship of the green-producing strains to hemolytic streptococcus is indicated, moreover, by the fact that the hemolytic streptococcus serum commonly manifests decided agglutinating power over them (Table 3).

The agglutination experiments show that the green-producing strains of streptococci from influenza are immunologically identical or closely related. If this is true, single highly agglutinable strains should absorb the specific agglutinins from the serum for all the rest. This has been found to be the case in a large number of tests. Strains isolated in the beginning of the epidemic absorb the agglutinins so that a large number of strains isolated recently are no longer agglutinated. The results with a number of these strains are given in Table 4. It will be noted that while the specific strain absorbed the agglutinins, Type II pneumococci which were not agglutinated, removed few or no antibodies.

TABLE 4.—SPECIFIC AGGLUTININ-ABSORPTION BY THE STREPTOCOCCUS FROM INFLUENZA

Mixtures (Dilution of Serum 1:40)	Strains											
	2698:2	2800:2	2874:13	3258:1	3265:4	3362:3	3370:4	3380	3403:2	3404	3412	3415:2
Serum Horse 15.....	4+	3+	3+	2+	2+	3+	2+	2+	4+	2+	2+	3+
Serum Horse 15 after treatment with pneumococcus II.....	3+	2+	3+	2+	2+	2+	2+	2+	3+	2+	2+	3+
Serum Horse 15 after treatment with streptococcus from influenza.....	0	0	0	+	+	0	0	0	+	0	0	+
Normal horse serum.....	0	0	0	0	0	0	0	0	0	0	0	0
NaCl solution.....	0	0	0	0	0	0	0	0	0	0	0	0

The symptoms and lesions of influenza have been closely simulated in guinea pigs by the intratracheal application of green-producing streptococci from influenza. The existence of a pandemic strain among the green-producing streptococci or diplostreptococci in influenza is shown by the immunologic studies summarized in this paper.

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## IV. Further Results of Prophylactic Inoculations\*

E. C. ROSENOW AND B. F. STURDIVANT

To determine the value of vaccination against disease, it is essential that the disease shall be one which a relatively large number of persons will develop unless protected, and that it be accompanied by serious consequences. These conditions were amply fulfilled during the pandemic of influenza. Moreover, the vaccine should contain the killed bacteria that produce symptoms and which are at least contributory to the cause of death. We have attempted, so far as possible, to fulfill this requirement by making a careful bacteriologic study of the disease, and by incorporating into the vaccine the important bacteria isolated. The epidemic was severe, and the need and the demand for vaccination were great; a large number of cases were available for bacteriologic study and to supply the proper strains for the vaccine. Vaccinations in large numbers during the past ten years with bacteria belonging to the group found in influenza have at least proved harmless, and in the case of pneumonia, prophylactic vaccinations have been successfully carried out by Wright, Lister, and Cecil and Austin. A splendid opportunity to study the effect of prophylactic inoculation was at hand. Owing to the foresight of the founders of the Mayo Foundation, necessary funds to meet the emergency were available. A large amount of the vaccine has been prepared and sent gratis on

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request to numerous physicians on condition that reports of the results be returned.

In a previous report,<sup>7</sup> the reasons for the use of a mixed vaccine containing, as far as possible, freshly isolated strains were discussed. It was pointed out that the streptococci, especially green-producing streptococci from influenza, have certain peculiar properties. The preliminary results, as reported from the use of this vaccine, indicate that considerable protection is afforded against influenza and especially against the accompanying pneumonia. Vaccinations were begun soon after the onset of the epidemic. The period of observation was six weeks. It is our purpose in this paper to emphasize essential points in the preparation of the vaccine, to present further results from its use, and to record certain immunologic experiments.

#### COMPOSITION AND PREPARATION OF THE VACCINE

Influenza bacilli were isolated in large numbers at the outset of the epidemic, but they were rarely found later in the epidemic. The small fraction of influenza bacilli included in the first few batches of vaccine were therefore omitted, and the vaccine was made to contain a proportionately higher percentage of the green-producing streptococci. In other respects, the original formula has been adhered to. The formula as used in almost all cases covered by the present report is given in Table 1.

TABLE 1.—FORMULA OF VACCINE

Pneumococci, Types I (10 per cent), II (14 per cent), and III (6 per cent.)	30 per cent
Pneumococci, Group IV and the allied green-producing diplo-streptococci described	40 per cent
Hemolytic streptococci	20 per cent
Staphylococcus aureus	10 per cent

The preparation of the medium, the method of cultivating and collecting the bacteria, and the procedure of standardizing the dose and killing the bacteria are described in the preliminary report.<sup>7</sup> The vaccine, it will be remembered, was made to contain approximately 5 billion bacteria for 1 c.c. Later, the concentration was made twice as great, and the quantity of liquid was reduced to one-half. The injections were given subcutaneously one week apart. The first dose of the concentrated vaccine (0.25 c.c.) contained 2.5

billion, the second (0.5 c.c.) 5 billion, and the third (0.75 c.c.) 7.5 billion bacteria. Considering the large size of these doses and the reactions obtained, the injections should not be given oftener than once a week in order not to overstimulate the mechanism of immunity.

The tendency of streptococci to undergo changes and to lose specific properties has been repeatedly emphasized by one of us. It was thought important that freshly isolated strains should be included in the vaccine. In Table 2 are given the culture generations of all the strains that have been used throughout the epidemic. The fermentation power was tested of fifty-seven strains of the green-producing streptococci included in the vaccine; only twenty-seven fermented inulin, and only eight were bile soluble.

TABLE 2.—CULTURE GENERATION OF BACTERIA FROM INFLUENZA AS USED IN THE VACCINE

Cultures	Green-producing streptococcus	Hemolytic streptococcus	Staphylococcus
Third generation or below.....	58	18	18
Fourth to tenth generation.....	95	20	8
Eleventh to twentieth generation.....	21	0	0
Total.....	174	38	26

The advantages which should come from the use of a lipovaccine, particularly when a series of strains needs to be included, have already been pointed out, and a simple method for the preparation in oil of a vaccine of the formula given in Table 1 has been developed and submitted for publication. A further study of the sputum and other material shows that of all the bacteria isolated, the somewhat peculiar green-producing streptococcus or diplostreptococcus is the most important. This organism is present in large numbers at the very outset of symptoms of influenza and of the accompanying pneumonia; it is commonly present after death. If the sputum or mass cultures are injected intraperitoneally into animals, they die, usually from invasion of the green-producing streptococci or pneumococci. If injected intratracheally in guinea pigs the picture of influenzal pneumonia is closely simulated. Immunologic experiments with the serum from a horse injected with one strain indicate that most of the strains are immunologically alike. The serum of cases of influenza develops agglutinating power over these strains.

TABLE 3.—AGGLUTINATING POWER OF THE SERUM OF PERSONS INOCULATED WITH SALINE VACCINE

Serums (dilutions 1:20)	Strains								
	492	1	3	2,568 <sup>1</sup> .2	2,604.2	3,048.3	2,874 <sup>1</sup> 3	2,575.2	2,608 <sup>1</sup> .2
2,542 24 hours before third dose saline vaccine.....	0	0	0	0	0	+	+	0	0
2,542 24 hours after third dose saline vaccine.....	0	0	0	0	0	+	+	0	0
2,542 48 hours after third dose saline vaccine.....	0	0	0	0	++	++	++	0	0
2,542 10 days after third dose saline vaccine.....	+	++	+	0	++	++	++	++	0
2,542 6 weeks after third dose saline vaccine.....	+	++	..	..	++	..	..	..	0
2,543 24 hours before third dose saline vaccine.....	0	0	0	0	+	0	0	0	0
2,543 24 hours after third dose saline vaccine.....	0	0	0	0	+	0	0	0	0
2,543 48 hours after third dose saline vaccine.....	+	0	0	0	++	0	++	0	0
2,543 10 days after third dose saline vaccine.....	++	+	0	0	++	++	++	+	+
2,543 6 weeks after third dose saline vaccine.....	++	+	0	0	++	++	++	+	0
2,545 24 hours before third dose saline vaccine.....	0	0	0	0	0	0	0	0	0
2,545 24 hours after third dose saline vaccine.....	0	0	0	0	0	0	0	0	0
2,545 48 hours after third dose saline vaccine.....	0	0	0	0	+	0	0	0	0
2,545 10 days after third dose saline vaccine.....	++	0	0	0	++	++	++	++	++
2,545 6 weeks after third dose saline vaccine.....	++	0	0	+	++	++	++	++	++
2,547 24 hours before third dose saline vaccine.....	0	0	0	0	0	0	0	0	0
2,547 24 hours after third dose saline vaccine.....	0	0	0	0	0	0	0	0	0
2,547 48 hours after third dose saline vaccine.....	+	0	0	0	+	+	++	0	0
2,547 10 days after third dose saline vaccine.....	++	0	+	+	++	++	++	0	0
2,547 6 weeks after third dose saline vaccine.....	++	0	+	+	++	++	++	0	+
3,075 normal.....	0	0	0	0	0	0	0	0	0
3,076 normal.....	0	0	0	0	0	0	0	0	0
NaCl.....	0	0	0	0	0	0	0	0	0



## AGGLUTINATING POWER

In Table 3 it is shown that the vaccine used possessed well marked antigenic powers. The strains S 1, 3, 2598<sup>2</sup>.2, 2604.2, 3048.3, and 2874<sup>3</sup>.3 were green-producing streptococci or pneumococci; 2575.2, a hemolytic streptococcus, and 2608<sup>3</sup>.2, a staphylococcus from cases of influenza. It will be noted that agglutinins appear in the serum on the tenth day and persist for six weeks. Table 3 shows, moreover, that the bacteria in the vaccine (492) used as the antigen in the first column were susceptible to agglutination. This vaccine was prepared three months previously and was kept in the ice chest. Most of the strains used as antigen in the experiment recorded in this table were not included in the vaccine used to immunize the persons whose serums were tested. All the green-producing streptococci were agglutinated, however, by the monovalent horse serum.

In Table 4 are given the results following the injection of a single dose of the lipovaccine (from 25 to 75 billions) in three persons. It

TABLE 4.—AGGLUTINATING POWER OF THE SERUMS OF PERSONS INOCULATED WITH LIPOVACCINE

Serums (dilutions 1:20)	Strains						
	3,271 <sup>1</sup> .3	3,296 <sup>1</sup> .2	3,331	3,332.2	3,334.2	3,334.2	3,342
3,074 normal.....	0	++	+	+	0	++	0
3,074 4 days after lipovaccine.	+	+++	++	++	+	++	0
3,074 10 days after lipovaccine	+++	++++	+++	++	++	+++	0
3,074 6 weeks after lipovaccine	++	+++	++	+	+	++	0
3,075 normal.....	0	++	0	0	+	0	0
3,075 4 days after lipovaccine.	++	+	0	0	+	++	0
3,075 10 days after lipovaccine	+	++++	+	+	++	++	0
3,076 normal.....	0	++	+	0	0	0	0
3,076 4 days after lipovaccine.	+	+++	+	0	+	0	0
3,076 10 days after lipovaccine	++	+++	++	0	+	0	0
3,076 6 weeks after lipovaccine	+++	++++	+	0	++	0	0
NaCl.....	0	0	0	0	0	0	0

may be noted that the amount of agglutination is greater than that following the injection of the saline vaccine, but here, as in the case following the injection of the saline vaccine, not all strains are equally susceptible to agglutination, and some are not agglutinated at all.

Table 5 shows the agglutinating power of various immune horse serums over strains of green-producing streptococci from influenza, strains included in the vaccine. The serum from Horse 15, immunized with one strain from the blood of a patient who died, has marked ag-

glutinating power over most of the strains. Of the thirty-three strains tested in this manner, twenty-five were agglutinated specifically by this serum. The results indicate clearly that among the green-producing streptococci, including Group IV pneumococci in influenza, there are strains which have a specific relationship, and that we were fortunate in successfully separating them from the ordinary *Streptococcus viridans* and including them in the vaccine long before the results of immunologic experiments were available.

The apparent protection against attacks of influenza noted in the preliminary report, difficult to understand at that time, now becomes rational.

#### METHOD OF SECURING DATA

In most instances the reactions were mild; about one person in each 100 reacted more severely. Some reacted severely to all three inoculations, others only to one or two. Persons coming down with a cold or with symptoms of influenza are often hypersensitive. Marked diffuse redness resembling erysipelas about the site of inoculation, with swelling and, later, marked induration, has occurred occasionally. In no instance were the symptoms alarming. The number of severe reactions is sufficiently large, however, to prevent general vaccination except at the time of an acute emergency. This is in accord with the experience of Cecil and Austin,<sup>2</sup> noted during prophylactic inoculations with pneumococci. An

TABLE 5.—AGGLUTINATING POWER OF VARIOUS IMMUNE HORSE SERUMS OVER STREPTOCOCCI INCLUDED IN THE VACCINE

Serums (dilutions 1:20)	Strains														
	2,347.19	2,349.13	2,350.16	2,531.14	2,532.4	2,534.11	2,557.2	2,604.2	2,618.2	2,684.16	2,698.3	2,710.1	2,769	2,800.2	2,825
Pneumococcus Type I.	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0
Pneumococcus Type II	++	0	0	+	0	+	0	0	0	++	0	0	0	0	0
Pneumococcus Type III	0	0	0	+	0	+	0	0	0	0	0	0	0	0	0
Horse 9.....	++	++	0	+	0	++	0	0	0	0	0	++	0	0	+
Horse 15.....	++	++	++	++	++	++	0	++	++	++	++	++	++	++	++
Normal horse.....	0	0	0	+	0	+	0	0	0	0	0	0	0	0	0
NaCl.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

outline for records of persons vaccinated was sent with each batch of vaccine and later a questionnaire. The questionnaire asked for the date of the onset of the epidemic, the date when the vaccine was first used, the week of the height of the epidemic, the week in which the greatest number of vaccinations were given, and the duration of the epidemic. The number of cases of influenza from the time the vaccinations were begun until the end of the epidemic, or up to May 1, and the number of deaths which occurred among the vaccinated and unvaccinated in the same period, in the practices of the physicians supplied with the vaccine, were asked. The reports of the use of the vaccine after the epidemic had disappeared were excluded. The period of observation in most instances was from four to five months.

In determining a safe criterion as to the value of the vaccine, we have purposely been unfair to the vaccinated group. The protection afforded among the vaccinated patients was measured from the day of the first vaccination, whereas, judging by the agglutination experiments, it should be calculated from about one week after the third injection.

There is another reason why we have arbitrarily decided to make our calculations from the day of the first vaccination. A procedure, calculated to protect against an epidemic disease, such as influenza, should have sufficient protective value when given after the onset of the epidemic to be measurable, for it is practically impossible to anticipate these epidemics and, moreover, persons will not present themselves for vaccination until the epidemic is at hand.

The questionnaire was arranged so as to yield information regarding the incidence of influenza, acute edema of the lungs, pneumonia, and empyema, and the deaths from acute edema of the lungs, pneumonia, empyema, meningitis, and encephalitis among the vaccinated and the unvaccinated. Separate reports including the foregoing points were asked for from institutions and in the cases of pregnant women. The impressions gained from the use of the vaccine regarding the severity of the disease if contracted following vaccination, and the effect, if any, which the vaccine had on certain chronic infections, such as bronchitis, sinusitis, myositis, and arthritis were asked for.

Many physicians were so overwhelmed during the height of the epidemic that accurate records could not be kept, and accordingly the reports containing accurate data are proportionately few. The

reports of 530 physicians were fairly complete, however, and these are summarized in Table 6. It is realized that there must necessarily be errors in the morbidity figures as reported to us, just as in the case of reports to boards of health. It is generally agreed that as influenza became more prevalent and less severe, a proportionately smaller number of cases were reported, and that all morbidity figures reported are well below the actual figures. The error, however, among the vaccinated and unvaccinated groups in the reports to us, should be approximately the same, and hence the figures should be comparable. Mortality figures, on the other hand, may be considered as fairly accurate.

## RESULTS OF INOCULATION

The total number of unvaccinated persons recorded in Table 6 represents the sum of the estimated clientele of the various physicians reporting the cases, and averages about 1,200 for each. It will be noted that the incidence of influenza, of acute edema of the lungs, of pneumonia following influenza, and the number of deaths from all causes among the vaccinated are consistently lower than that among the unvaccinated. Moreover, the incidence of disease and deaths is lowest in the group of 93,476 persons who were vaccinated three times. The reports included in this table were from many states, but the largest number came from Iowa, Minnesota, and Wisconsin. Thirteen thousand, six

TABLE 6.—RESULTS AS REPORTED IN QUESTIONNAIRES FROM ALL SOURCES

Groups	Total number	Incidence for 1,000 persons									
		Disease				Deaths					
		Influenza	Acute edema of lungs	Pneumonia	Empyema	Acute edema of lungs	Pneumonia	Empyema	Meningitis	Encephalitis	Total deaths
Vaccinated once.....	26,936	118.2	3.1	8.7	0.29	0.14	2.6	0.07	0.18	....	3.0
Vaccinated twice.....	23,348	97.0	0.77	3.04	0.17	0.47	1.9	0.04	0.21	....	2.62
Vaccinated 3 times.....	93,476	87.9	0.8	4.4	0.18	0.18	1.2	0.0	0.05	....	1.43
Not vaccinated.....	345,133	281.8	4.4	21.0	0.93	1.7	2.37	0.07	0.15	0.03	8.55

hundred fifty persons inoculated and 2,083 who died were grouped according to age by decades. The curves indicating the percentage in each run roughly parallel.

The largest number of inoculations were given and the largest number of deaths occurred between the ages of 11 and 40. The percentages of the former in these three decades were 23, 19, and 21, of the latter 13, 29, and 23, respectively. Through the cooperation of the Board of Health of Minnesota we were able to check the results as reported to us with the morbidity and mortality figures as reported to them. Reports on a considerable number of vaccinations were received from Brown, Chippewa, Clay, Dodge, Fillmore, Goodhue, Houston, Itasca, Lesueur, Lyon, Mower, Olmsted, Rice, Stearne, Steele, Wabasha, Waseca, Watonwan, and Winona counties. The total estimated population of these counties is 472,584. The total number of cases of influenza in these counties reported to the board of health from the beginning of the epidemic until May 1 is 30,763, or sixty-five for each thousand. This is admittedly a low figure. The total mortality rate as reported to the board of health during this time is 4.2. The mortality rate, excluding the deaths which occurred in the respective counties prior to the date of the first vaccinations, is 3.2 (Table 7). The figures in the table indicating the cases and the deaths as reported to us are believed to be more accurate. The mortality rate, exclusive of that of the Mayo Clinic, in the 17,532 persons vaccinated three times is only one fourth of that reported to the board of health. Moreover, the total number of deaths among the vaccinated, including the persons inoculated only once and twice, is 1.6 for 1,000, or half the mortality rate as reported to the board of health during the same period of time. When we consider the fact that the deaths in each group were counted from the time the first vaccinations were given, which is really unfair to the vaccine, and the fact that our figures include all pneumonias, while those of the board of health included only the influenzal pneumonias, there seems little doubt that the difference must be due to the protection afforded by the vaccine. The figures given in Table 8 for Olmsted County, where about one third of the population was vaccinated, exclusive of the Mayo Clinic and the state hospital, are similar to those obtained elsewhere. The incidence of disease and the death rate among those vaccinated three times are well below those of the unvaccinated.

TABLE 7.—RESULTS AS REPORTED IN QUESTIONNAIRES FROM NINETEEN COUNTIES IN MINNESOTA EXCLUSIVE OF THE MAYO CLINIC

Groups	Total number	Incidence for 1,000 persons							
		Disease				Deaths			
		Influenza	Acute edema of lungs	Pneumonia	Empyema	Acute edema of lungs	Pneumonia	Empyema	Total deaths
Vaccinated once.....	4,828	115.	0.4	8.28	0.0	0.0	0.2	0.0	0.2
Vaccinated twice.....	4,029	88.3	0.74	3.7	0.47	0.47	1.9	0.0	3.2
Vaccinated 3 times.....	17,532	102.8	0.17	4.2	0.22	....	0.62	....	0.8
Not vaccinated.....	36,100	373.5	1.35	20.4	0.6	1.4	4.0	0.13	6.35
As reported to State Board of Health.....	472,584	65.3	....	....	....	....	....	....	3.2*
(Estimated population)									

\* Exclusive of deaths which occurred prior to the use of the vaccine and exclusive of the Mayo Clinic cases.

TABLE 8.—RESULTS IN OLMDSTED COUNTY EXCLUSIVE OF MAYO CLINIC AND STATE HOSPITAL FOR INSANE

Groups	Total number	Incidence for 1,000 persons							
		Disease				Deaths			
		Influenza	Acute edema of lungs	Pneumonia	Empyema	Acute edema of lungs	Pneumonia	Empyema	Total deaths
Vaccinated once.....	2,424	100.2	0.0	6.1	0.0	0.41	2.8	0.0	3.2
Vaccinated twice.....	1,021	291.8	2.9	0.0	1.9	0.0	4.8	0.0	6.7
Vaccinated 3 times.....	9,300	41.0	0.18	3.9	0.43	....	0.43	0.21	0.64
Not vaccinated.....	8,700	248.0	3.2	13.1	0.45	0.9	2.6	0.45	4.0

The results obtained in institutions in which the conditions among the vaccinated and the unvaccinated were comparable are summarized and given in Table 9 in order still further to check the figures. The number of persons in most of the institutions included (fifty-three in all) was small. The opportunity for accurate observation was, therefore, favorable. The institutions included factories, personnel of hospitals, schools, and offices. The proportion of the vaccinated and unvaccinated varied between wide limits. The period of observation in the two groups was the same. The incidence of disease and the number of deaths in almost all instances were lower in the vaccinated than in the unvaccinated. The total average, as given in Table 9, compares favorably with that of the others. The death rate among the vaccinated is decidedly lower than that among the unvaccinated.

TABLE 9.—RESULTS OF PROPHYLACTIC INOCULATION IN INSTITUTIONS WHERE THE CONDITIONS AMONG THE VACCINATED AND UNVACCINATED WERE COMPARABLE

Groups	Total Number	Incidence for 1000 persons					
		Disease				Deaths	
		Influenza	Acute edema of lungs	Pneumonia	Empyema	Acute edema of lungs	Pneumonia
Vaccinated 3 times...	8,306	31	0.1	1.0	0.2	0.0	0.5
Not vaccinated.....	9,388	200	0.5	12.0	0.6	0.4	5.5

The results given in the tables are in agreement with the numerous reports received by which it appeared that the vaccine had afforded striking instances of protection. In a few cases no protection seemed to be afforded, but in most of these the vaccinated persons contracted the disease a long time after the inoculations. It is fully realized how difficult it is to judge just how much protection was conferred in many of these instances, and how much of the apparent protection was merely coincidental. But a careful study of the reports from 303 physicians, some of which were the result of careful observation, forces the conviction that real protection, especially against pneumonia, was afforded. In some of these instances most of the observations were made within six weeks to two months after the vaccine was given.

It was thought that the injection of large doses of a mixed vaccine might have some effect on certain chronic infections, especially of the

respiratory tract. A summary of the reports shows that 961 persons with chronic bronchitis were benefited and that 38 were made worse. The reports show that 127 persons with chronic sinusitis were benefited and 4 made worse. Improvement was noted in 121 persons having myositis and in 129 with arthritis, while in one of the former and in 22 of the latter the symptoms were aggravated. These figures are not considered to be especially significant but worthy of record. They are in accord with our own observations.

#### RESULTS OF PROPHYLATIC INOCULATION IN PREGNANCY

The results of vaccinations in pregnant women as reported in the questionnaires are summarized in Table 10. The incidence of disease and that of miscarriages and the mortality rate are consistently lower among those vaccinated than among those not vaccinated. The mortality (20 per cent) of the unvaccinated pregnant women who developed influenza is somewhat lower than that reported from similar statistical studies by Bland and by Harris. They report a mortality of 37.7 per cent and 27 per cent respectively. The mortality of 12 per cent in the 997 pregnant women inoculated in our series is in sharp contrast and calls for a further trial of this measure.

Almost from the beginning of the epidemic of influenza, patients who registered at the Mayo Clinic were advised to be vaccinated. From October 1 to May 1, 55,189 patients registered. Of these, 2,542 were vaccinated once, 1,030 twice, and 1,850 three times, a total of 5,422. A reliable morbidity and mortality rate for each thousand of the

'19-60

TABLE 10.—RESULTS OF PROPHYLACTIC INOCULATION IN PREGNANCY

Groups	Total number	Incidence for 1,000 persons										Mortality of those who developed influenza
		Disease					Deaths					
		Influenza	Acute edema of lungs	Pneumonia	Erysipema	Miscarriage	Acute edema of lungs	Pneumonia	Erysipema	Meningitis	Total deaths	
Vaccinated 3 times...	997	109.3	17.0	27.0	.....	14.0	2.0	12.0	.....	.....	14.0	12 per cent.
Not vaccinated.....	3,656	294.6	17.7	80.4	0.82	46.2	12.3	46.2	0.54	0.82	59.9	20 per cent.



vaccinated and unvaccinated could not be determined because such a large percentage of patients remained in Rochester for too short a time.

It was thought that a study of the cases of influenza admitted to the hospitals might, however, be worth while. Of these, 749 were undoubted cases of influenza, and were analyzed from various stand-points. Fifty-nine of the patients were vaccinated once; 24 twice, and 57, three times, while 609 were not vaccinated. The incidence of pneumonia and the deaths from pneumonia in these groups are recorded in Table 11. The average interval between the vaccinations and the onset of influenza was nine days in those vaccinated only once, twenty-six days in those vaccinated twice, and forty-five days in those vaccinated three times. The average temperature was more than one degree higher in the unvaccinated than in the vaccinated, and the average duration of fever nearly two days longer. The percentage incidence of pneumonia in those vaccinated three times was 21; in those not vaccinated, 57, while the percentage of deaths from pneumonia was 5 in the former group and 22 in the latter. The mortality from pneumonia of those vaccinated only once and those vaccinated twice is also well below that of the unvaccinated. The mortality figure in the unvaccinated is abnormally high because only the patients with relatively severe attacks were admitted to the hospitals.

TABLE 11.—RESULTS IN PATIENTS WITH INFLUENZA ADMITTED TO HOSPITALS IN ROCHESTER

Groups	Cases of influenza	Incidence of pneumonia	Deaths from pneumonia, per cent
Vaccinated once.....	59	39	10
Vaccinated twice.....	24	95	12
Vaccinated 3 times.....	57	21	5
Not vaccinated.....	609	57	22

The greater tendency to the development of pneumonia in influenza among the unvaccinated group as observed in this series is in keeping with the lower incidence of this complication (4.7 per cent) in 11,325 cases of influenza in which the vaccine was given after the onset of the symptoms, as compared with the incidence (8.7 per cent) in 41,788 cases in which the vaccine was not used. The average

mortality in the cases in which the vaccine was used in treatment was 1.4 per cent; in those not treated it was 2.1 per cent.

From these results considerable weight may be attached to the opinion of nearly all the 430 physicians who have used the vaccine and who have reported on this point, an opinion in agreement with our own observations, that is, that the attacks of influenza if contracted following vaccination are milder and of shorter duration.

### SUMMARY

The immunologic and animal experiments reported elsewhere<sup>8</sup> indicate that the mixed vaccine used by us contained the important bacteria as they occur in influenza and the accompanying pneumonia, and that a relatively large number of strains of the green-producing streptococci which appear to have a specific relationship to the initial attack were included. The reports included results obtained under the most varied conditions, from many communities covering a wide range of territory. In some communities the mortality rate was excessively high, in others comparatively low. The number of persons inoculated is sufficiently large to make the statistical figures fairly accurate. The period of observation was from three to seven months. The incidence of influenza and pneumonia as reported to us is probably far from exact, but the percentage of error should be about the same in the vaccinated and unvaccinated groups. Indeed, if a difference exists, the number of cases reported among the vaccinated might be expected to be proportionately higher because, even though no protection was promised, the fact that influenza occurred after the vaccinations were taken would naturally lead to a higher percentage of reports to the physician who gave the inoculations. The average incidence of influenza and pneumonia in the group inoculated three times is about one-third that of the uninoculated group.

The average mortality rate in the uninoculated, as reported to us, approximates the mortality rate (5.4 per cent) of sixteen large cities of the United States as given in *Public Health Reports* for February 7. The average mortality rate in the group inoculated three times is about one-fifth that of the uninoculated. A definite although a smaller degree of protection appeared to be afforded to those who took only one or two inoculations. From a study of a series of hospital cases of influenza it is found that the tendency to the development of pneu-

monia in the vaccinated is about one third as great as among the unvaccinated, and that the mortality in the former is about one fifth as great as in the latter. The number of completed vaccinations in pregnant women is not large enough to give exact figures, but the results indicate clearly that a definite degree of protection was afforded in this group of individuals.

It appears from all the facts at hand that by the use of a properly prepared vaccine it is possible to rob influenza of some of its terrors.

The preliminary results from the use of more than 500 doses of this vaccine suspended in oil, the immunologic studies and the results from the use of pneumococcus lipovaccine reported by Fennel and by Cecil and Vaughan suggest strongly that both the degree of protection and the duration of the immunity may be materially increased by the use of lipovaccine over that reported in this paper from the use of the saline vaccine.

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# THERAPEUTIC EFFECTS OF A MONOVALENT ANTISTREPTOCOCCUS SERUM IN INFLU- ENZA AND INFLUENZAL PNEUMONIA

E. C. ROSENOW

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In a previous publication<sup>1</sup> the importance has been emphasized of a somewhat peculiar diplostreptococcus in influenza and influenzal pneumonia. This organism has been found quite constantly in a large series of cases. By intratracheal application in guinea pigs, the symptoms and the pathologic picture of influenza have been closely simulated.<sup>2</sup> The existence of a pandemic strain among the green producing diplostreptococci in influenza has been demonstrated by immunologic studies.<sup>3</sup> A lower incidence of influenza and influenzal pneumonia occurred in persons inoculated prophylactically with a vaccine containing a high percentage of these strains than in persons not so inoculated.<sup>4</sup> Owing to these findings, a monovalent serum was prepared in a horse by injecting in increasing doses one of these strains isolated from the blood in a fatal case.

In one of the reports<sup>3</sup> the following statement was made: "In studying the agglutinating power of various immune serums over strains from the sputum daily or on alternate days throughout the disease, it has been found that the strains are agglutinated specifically by this serum throughout the course in typical cases in which the patients recover without developing pneumonia or in which the pneumonia is of short duration. This is not usually true, however, of patients with protracted or recurring pneumonia, especially those who die. In these there may be a shifting of agglutination to pneumococcus serums, Types II or III, to hemolytic streptococcus serum, or, more often, they may not be agglutinated by any of the serums."

In this paper I wish to record the results obtained in the treatment of influenza and influenzal pneumonia with this serum in patients in whom in addition to cultural tests the immunologic condition of the streptococcal flora of the sputum was studied. This study was made possible through the willing coöperation of Dr. H. M. Conner and other physicians in charge of the cases treated.

The serum was used in only undoubted and, with one exception, severe cases. All injections were made slowly intravenously. The amount injected at one time ranged from 25 c.c. to 100 c.c. In some

instances a desensitizing dose of 1 c.c. was given one hour previously. Altogether 12 patients were given the serum. These may be conveniently divided into three groups according to the agglutination tests and therapeutic results.

*Group 1.*—Four patients belonged in this group. The sputum of all contained predominating numbers of green-producing streptococci which were agglutinated specifically by the monovalent serum. All four showed marked improvement, and all recovered promptly following the serum treatment. Three of these had the initial influenzal attack, and one a recrudescence at the time of the serum treatment. The lung findings in all of these remained limited; no one of the patients developed outspoken signs of extensive consolidation. In at least 2, the improvement seems definitely attributable to the serum since the lung findings and symptoms were on the increase at the time of the serum treatment (Cases 1, 2, and 3, and Chart 1).

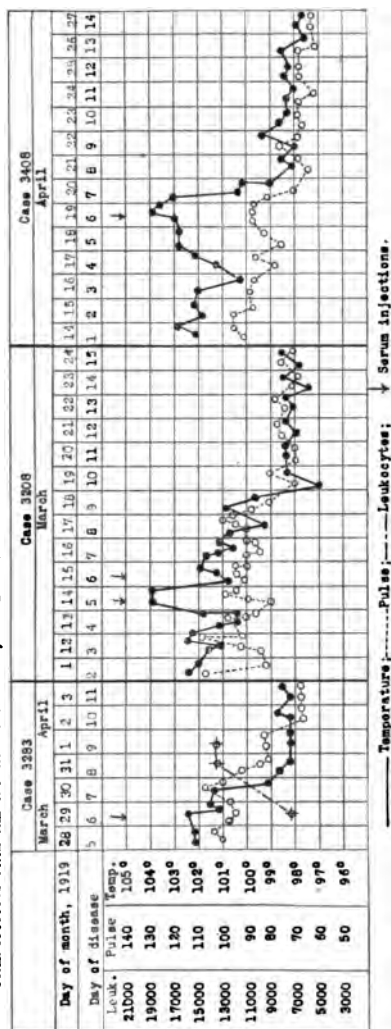
*Case 1 (3283).*—Mrs. H. C. L. came to the Clinic March 11, 1919 on account of nervousness, general weakness, fluttering of the heart, and profuse menstruation. The symptoms followed a severe attack of influenza in October. Family and previous history were negative. An examination revealed a pelvic tumor for which a hysterectomy was advised.

The patient was admitted to the Isolation Hospital March 28, with symptoms of influenza. She had been taken ill five days previously with moderate headache, aching in the arms and back, sore throat, cough, and slight nausea. These symptoms grew gradually less severe until the day before admission to the hospital, March 27, when she became worse with general aching, chilly sensations in the back, but no distinct chill or fever. Examination showed diffusely red throat, coated tongue, cyanosis, and crackling râles over the bases of both lungs, especially on the right side. The heart findings, blood pressure, and urine were normal. The sputum on the day of admission was slightly blood streaked. No evidence of consolidation was noted at any time. A culture of the sputum showed predominating numbers of green-producing streptococci and a few staphylococci, and the primary culture in dextrose-blood broth was agglutinated specifically by the serum from Horse 15 (Table 1). March 29, the patient was given 50 c.c. of this serum, the aching disappeared during the course of the day, the cough lessened, the following day the temperature dropped perceptibly and became normal (Chart 1).

The leukocyte count was 7300 the day following admission and rose to 13,500 March 31 and April 1. The patient made an uneventful recovery, and was operated on April 24 by Dr. C. H. Mayo. A sub-total abdominal hysterectomy was performed and multiple fibromas

Chart 1

TEMPERATURE, PULSE AND LEUKOCYTE CURVES IN THREE PATIENTS IN WHOM SPECIFIC AGGLUTINATION OF THE GREEN-PRODUCING STRAPTOCOCCUS FROM THE SPUTUM WAS OBTAINED, AND IN WHOM MARKED IMPROVEMENT FOLLOWED INJECTION OF THE MONOVALENT SERUM



ability to sleep, sore throat, and cough. The illness had begun the previous day with chilly sensations but there had been no distinct chill. On examination the patient was found well nourished; he showed moderate cyanosis of the lips and fingernails, was mentally apathetic, although he complained of inability to sleep. The throat was diffusely red. The tonsils were also injected, and the tongue was heavily coated. The night of March 13 the patient had repeated severe hemorrhage from the nose which continued at intervals the following day. The lung findings were negative until March 17 when a small area of dullness was found at the inferior angle of the left scapula with slightly increased vocal fremitus and suggestion of bronchial breathing. Later in the day dullness at the left base of the lung, fine crepitant râles in showers, and distinct bronchial breathing, especially at the inferior angle of the scapula near the spine, were noted. The sputum at first was mucopurulent, but March 13 it became serous in character and streaked with blood. There was marked leukopenia (Chart 1). Blood-agar-plate cultures of the sputum obtained March 13, 15, and 17 showed countless numbers of green-producing streptococci, a few staphylococci, but no hemolytic streptococci nor influenza bacilli. A blood culture made March 12 was negative. Dextrose-blood-broth cultures of the green-producing streptococcus isolated directly from the sputum March 13 and from the lung of a guinea pig injected intratracheally with the sputum were agglutinated specifically by the serum of Horse 15 (Table 1). March 14 the patient's condition was very serious. Cyanosis was increasing, the sputum became more bloody and frothy, mental apathy was worse, and prostration and epistaxis were marked. In the afternoon the patient was given, intravenously, 60 c.c. of the serum. The hemorrhage from the nose stopped, the patient's general condition became much better, and he was brighter mentally soon after the injection. The following day the injection of serum was repeated. The temperature dropped gradually to normal, and he made an uneventful recovery (Chart 1). The effect of the serum in this case appeared strikingly favorable. The improvement was probably due to the serum and not coincident, since the symptoms and lung findings were on the increase at the time the serum was given. The patient developed a slight urticarial rash ten days later. This patient was one of a group of 5 who came to Rochester from the same locality and who had severe attacks of influenza within a few days of each other after their arrival in Rochester; 2 of the patients died.

**Case 3 (3408).—**A. H., a man of middle age, entered the hospital April 14, 1919. He complained of severe aching, headache, malaise, weakness, sore throat, and slight cough. General examination showed moderate cyanosis, without manifest dyspnea, mental apathy, a diffusely red throat, and coated tongue. The chest findings were negative on the day of admission, but bubbling râles over both chests were elicited posteriorly April 15, 16, 17, and 18. The leukocyte count April 15 was 4700. The sputum obtained April 18 was mucopurulent. The cultures showed countless numbers of staphylococci and a moderate number of rather moist, spreading, green-producing and hemolytic streptococci. A blood culture made the following day proved negative. The primary culture of the washed sputum in dextrose-blood-broth was agglutinated specifically by the serum of Horse 15 (Table 1). April 19, 25 c.c. of the serum were injected intravenously, following which there was a rapid drop in temperature and pulse rate, and marked improvement in the general condition of the patient who recovered promptly thereafter.

**Group 2.**—This group included 3 patients treated with the serum, all 3 of whom showed marked improvement following injection of the serum during the initial attack of influenza when the green-producing streptococcus from the sputum was agglutinated specifically by the monovalent serum, but who later developed bronchopneumonia due to green-producing streptococci that were not specifically agglutinated by this serum or by any of the immune serums tested (Table 1, Cases 4 and 5, and Chart 2).

**Case 4 (3282).—**Mrs. A. K., aged 48, came to the clinic on account of recurrence of an abdominal tumor which had been removed two years before. She was admitted to the Isolation Hospital March 28, 1919; she stated that she had become ill the day previously with a severe chill, sore throat, headache, and severe general aching. The lips and fingernails were cyanotic, the patient was short of breath, even when lying quietly in bed, and abundant crepitant râles were found posteriorly at the left base of the lung and on the right side. A culture of the sputum obtained on the day of admission showed a large number of staphylococci and green-producing streptococci, and duplicate cultures in dextrose-bloodbroth were agglutinated specifically by the serum of Horse 15 (Table 1). March 29 and 30 she was given, intravenously 80 c.c. and 60 c.c., respectively, of the serum of Horse 15. The general condition of the patient improved following both injec-





pulse was rapid, and a sharp rise in leukocyte count occurred. On the day following the rise of temperature the patient developed an urticarial rash covering the entire body. With increase in temperature, dullness, bronchovesicular breathing, and crepitant râles developed over the right side below the angle of the scapula. A culture of the sputum on the first day of normal temperature following the injection of the serum showed countless numbers of green-producing streptococci and staphylococci. The primary culture in dextrose-blood-broth was again agglutinated specifically by the serum of Horse 15. No cultures of the sputum were made subsequently. During the latter part of the attack of pneumonia, as the pulse rate crossed the temperature line (Chart 2), the patient's condition was extremely critical for a number of days, but she finally made a complete, although slow, recovery.

Case 5 (3338).—Mrs. R. S., aged 39, housekeeper, entered the Isolation Hospital April 5, 1919. Three days before the patient felt chilly, could not get warm, ached moderately, and was stiff in the joints and muscles. Two days afterward she developed a cough with slight sore throat, and a moderately severe headache. The patient, when quiet in bed, appeared quite well, but the lips and fingernails were decidedly blue. The examination of the chest was negative. The morning of April 7 a small area was found of slightly decreased resonance, bronchovesicular breathing, and a few râles below the angle of the left scapula near the posterior axillary line. The evening of April 8, crackling râles were heard on both sides in the lower axillæ and posteriorly. The morning of April 9 there were impaired resonance and crackling râles over the left base behind and at the side, and crackling râles over the right base posteriorly. The sputum was blood tinged and serous. By evening there was dullness over both lower lobes, but no definite bronchial breathing, while crackling râles were heard over the entire chest. A culture of the sputum on the seventh showed countless numbers of staphylococci and green-producing streptococci, a few hemolytic streptococci, and a moderate number of influenza bacilli. The primary culture in dextrose-blood-broth of the washed sputum obtained April 7 and 9, and of a throat swab, showed almost pure cultures of green-producing streptococci which were agglutinated specifically by the serum of Horse 15. Accordingly the patient was given intravenously 100 c.c. of serum April 9 and 10, respectively. The general condition improved fol-

lowing both injections, the cyanosis became less marked, the expectoration diminished, and a drop in temperature and pulse rate occurred, the temperature reaching normal the day after the second injection (Chart 2). The temperature remained normal for two days and then began to rise again, as evidence of a new involvement of the lung developed. The pulse rate remained high, and continued unusually high throughout the fatal recurrence. Cultures of the sputum obtained April 11, 13, 17, and 18 showed countless numbers of staphylococci, green-producing streptococci, an increasing number of hemolytic streptococci, and a few influenza bacilli. The green-producing streptococci, however, were no longer agglutinated specifically by the serum of Horse 15 (Table 1). The leukocyte count was persistently low throughout the first attack of fever, and at the onset of the recrudescence, but it then rose to a high point, the maximum (43,000) being reached on the sixth day. The two subsequent days the leukocytes diminished markedly and the patient died on the following day from what appeared to be cardiac failure from an overwhelming toxemia. After death the lung showed green-producing streptococci, hemolytic streptococci, and staphylococci, but no influenza bacilli. Duplicate cultures in dextrose-blood-broth of the lung exudate after death showed hemolytic streptococci which were agglutinated by the antihemolytic streptococcus serum from Horse 9. The reinfection in this case was clearly due to streptococci which culturally were identical, but which immunologically were unlike those found during the initial attack. The anatomic diagnosis made at necropsy was: "Unresolved influenzal bronchopneumonia; marked enlargement of the tracheobronchial lymph nodes; purulent hemocatarrhal tracheal bronchitis; bilateral serofibrinous pleuritis; marked engorgement of the venous trunks of the body; petechial hemorrhages in the lining of the stomach and duodenum; hemorrhagic cystitis; and marked hyperplasia of the spleen."

*Group 3.*—This group consisted of 5 cases in which no improvement followed the injection of the serum. In none of these was specific agglutination obtained at the time of the serum treatment, and all died. In one case (Case 3276) the agglutination of the streptococcus isolated from the sputum shifted from the serum of Horse 15 to Type III pneumococcus serum. In another case (Case 3341) agglutination occurred in Type II pneumococcus and hemolytic streptococcus

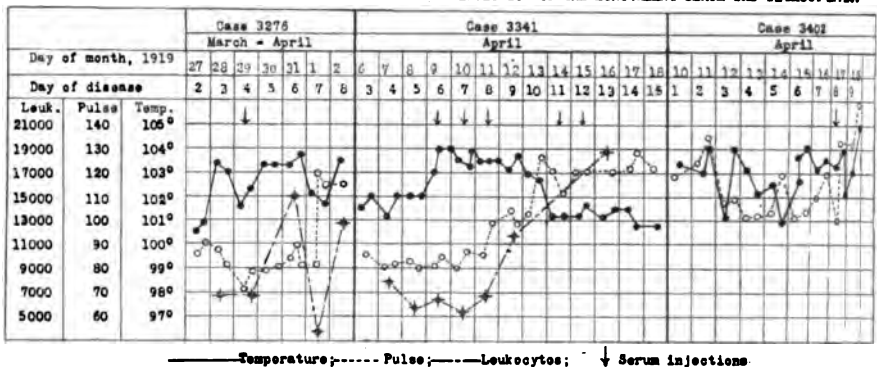
serums. In the third case (Case 3402) the sputum showed hemolytic streptococci which were not agglutinated by any of the serums (Table 1). In 2 cases in this group countless numbers of green-producing streptococci were found in the sputum which were not agglutinated by any of the serums, and the patients were moribund at the time of the serum treatment. Cases 6, 7, and 8 illustrate the conditions found in this group of cases.

Case 6 (3276).—E. I., aged 36, a farmer, was admitted to the Isolation Hospital March 27, 1919. The day before fever had developed with backache, general aching, headache, dry throat, cough, and marked weakness. March 28 the throat was congested; an examination of the chest was negative except for a few scattered crackling râles. March 29 crackling râles and decreased resonance were found at the base of the left lung. The sputum was moderately bloody. In the afternoon the patient was given 50 c.c. of serum from Horse 15; the injection had no effect. April 1 there were definite signs of pneumonia on the left side, especially below the angle of the left scapula. The sputum was very frothy and bloody. The patient's condition grew rapidly worse. Cyanosis and dyspnea increased. The patient died from typical hemorrhagic pulmonary edema April 2. The leukocyte count was low at first, but it rose to 15,000 March 31, and with the overwhelming toxemia showed a marked drop to 3500 April 1, with another slight increase on the day of death (Chart 3). Cultures from the sputum obtained March 28 showed countless numbers of moist, spreading, green-producing streptococci, a few staphylococci, but no hemolytic streptococci nor influenza bacilli. The primary culture in dextrose-blood broth of the washed sputum obtained March 28, and of the blood of a mouse, dead from intraperitoneal injection of sputum, were agglutinated specifically by the serum of Horse 15. On the contrary, the primary dextrose-blood broth culture of the washed sputum, and of the moist, spreading, greenish colony of streptococci from the sputum March 30 was agglutinated specifically by Type III pneumococcus serum. The primary culture of the sputum obtained April 2 was agglutinated slightly but equally by Type III pneumococcus serum and antihemolytic streptococcus serum from Horse 9 (Table 1). The colonies on blood agar from the dextrose-blood-broth on all the days showed no change and resembled closely Type III pneumococci, but they were not so elevated, and not so mucoid in character as *Pneumococcus mucosus*.

**Case 7 (3341).—J. R. W.,** aged 38, undertaker, was admitted to the Isolation Hospital April 6, 1919. His illness had begun two nights before with a severe chill, vomiting, fever, backache, aching in the knees, general aching, slight nose bleed, and sore throat. These symptoms were still present on admission. The patient coughed and expectorated mucopurulent sputum. He was definitely short of breath and cyanotic. An examination of the chest was negative except for a few scattered râles. April 7 there were decreased resonance and decreased breath sounds below the angle of the left scapula; the next day decreased resonance and breath sounds and a few crackling râles at the right base behind. April 9 very definite signs of

Chart 3

TEMPERATURE, PULSE AND LEUKOCYTE CURVES IN THREE PATIENTS IN WHOM SPECIFIC AGGLUTINATION OF STREPTOCOCCI FROM THE SPUTUM WAS NOT OBTAINED AND IN WHOM THE INJECTION OF THE MONOVALENT SERUM WAS WITHOUT EFFECT



a pneumonia were found on both sides. The sputum became very bloody and serous. Cultures of the sputum and throat swab obtained April 7 and 9 showed countless numbers of green-producing streptococci and staphylococci. April 12 the cultures showed countless numbers of staphylococci and a moderate number of green-producing streptococci, and larger, more moist spreading colonies resembling Type III pneumococci. The primary culture in dextrose-blood broth of the tonsil swab April 8 and sputum April 9, 11, and 13 were not agglutinated specifically by the serum of Horse 15. Fermentative reactions showed that the green-producing streptococci from the sputum fermented inulin. The cultures of the sputum obtained April 9 and 11 were agglutinated specifically by Type II pneumococcus serum; those on the following day by Type II, and hemolytic streptococcus serum (Table 1). The afternoons of April 9 and

TABLE 1.—AGGLUTINATION EXPERIMENTS WITH CULTURES FROM THE SPUTUM IN CASES OF INFLUENZA AND INFLUENZAL PNEUMONIA IN WHICH IMMUNE SERUM WAS USED

Case	Date on which sputum culture was made	Condition of culture at time of agglutination test. Dextrose-blood-broth inoculated with	Antiserums					Controls	
			Pneumococcus			Streptococcus		Normal horse serum	Na-Cl solution
			I	II	III	Hemolytic of Horse 9	Green-producing of Horse 15		
3208	3-13-19	Single green colony streptococcus	0	0	0	0	+++	0	0
		Green-producing streptococcus after one animal passage.....	0	0	0	++	++++	0	0
		Green-producing streptococcus in third generation after one animal passage.....	+	+	+	+	+++	0	0
	3-28-19	Washed sputum.....	0	0	0	0	+++	0	0
		Blood of mouse dead from intraperitoneal injection of sputum.							
		Pure green streptococcus.....	++	++	++	++	++++	++	0
3276	3-30-19	Washed sputum.....	0	+	+++	+	++	+	0
		Blood of guinea pigs injected intratracheally with moist, spreading greenish colony of streptococcus from sputum....	0	0	+++	0	0	0	0
	4- 2-19	Washed sputum.....	0	0	++	++	0	0	0
3282	3-30-19	Washed sputum.....	0	+++	+++	+++	++++	0	0
	4- 2-19	Washed sputum.....	0	++	+	++	+++	0	0
3283	3-30-19	Washed sputum.....	0	0	0	0	+	0	0
		Single colony moist green streptococcus.....	0	+	0	+	++	0	0
	4- 7-19	Washed sputum.....	0	0	0	++	++++	+	0
	4- 8-19	Swab from throat.....	0	0	0	0	+	0	0
	4- 9-19	Washed sputum.....	0	0	0	+	++	0	0
	4-11-19	Washed sputum.....	0	++	0	++	0	0	0
3338	4-13-19	Washed sputum.....	+	+	+	+	+	+	+
		Single colony green-producing streptococcus from sputum....	+	0	+	++	++	+	0
	4-16-19	Washed sputum.....	0	0	0	0	0	0	0
	4-17-19	Washed sputum.....	0	0	0	++	++	0	0
	4-25-19	Exudate right lung (hemolytic streptococci).....	0	++	0	+++	0	++	0
		Exudate right lung (hemolytic streptococci).....	+	+	+	+++	+	+	0
	4- 8-19	Tonsil swab.....	0	0	0	0	0	0	0
3341	4- 9-19	Washed sputum.....	0	+++	0	0	++	0	0
	4-11-19	Washed sputum.....	0	+++	++	++	++	0	0
	4-12-19	Single colony green streptococcus	0	+++	0	+++	++	0	0
3402	4-17-19	Throat swab.....	0	0	0	0	0	0	0
		Washed sputum.....	+	+	+	+	+	+	+
3408	4-18-19	Washed sputum.....	0	0	0	0	++	0	0

10, 100 c.c. of serum from Horse 15 were injected intravenously without effect. April 11 and 14 injections of polyvalent antipneumococcus serums were given without effect. April 13 the urine showed a large amount of albumin and some red blood corpuscles. April 15 the patient was growing worse. He was bled 250 c.c., and was then given intravenously 250 c.c. of blood of a convalescent influenza patient, likewise without effect. The leukocyte count ranged from 5500 in the earlier part of the attack to 19,200 in the later (Chart 3). The patient died April 18. The anatomic diagnosis was bronchopneumonia; chronic cystitis with exacerbation; chronic parenchymatous nephritis; and old tuberculous abscesses of the left lower lobe.

Case 8 (3402).—Mrs. T. O. McK. entered the hospital April 11, 1919; she complained of severe aching, fever, sore throat, and cough; she was toxic, cyanosed, and expectorated a small amount of mucopurulent sputum. The lung findings were negative; the heart showed mitral endocarditis with stenosis. April 14 and 15 crackling râles were elicited over both sides of the chest posteriorly, together with auricular fibrillation. April 16 the findings were definite for a pneumonia of the left base. April 17 the expectorations became bloody, and profuse; the cyanosis and dyspnea increased. An injection of the serum of Horse 15 had no apparent effect (Chart 3), and the patient died April 18 with signs of acute hemorrhagic pulmonary edema. The sputum obtained April 17 showed countless numbers of hemolytic streptococci, staphylococci, and a few green-producing streptococci, but no influenza bacilli. The primary cultures in dextrose-blood broth of a throat swab and washed sputum were not agglutinated by any of the serums (Table 1).

#### DISCUSSION

Of the 12 patients treated, all but one were seriously ill at the time of serum treatment. Five recovered and 7 died. Three of the patients who died were practically moribund at the time of the serum treatment and good effects could scarcely be expected. In 2 of the others, green-producing streptococci immunologically different from the strain with which the serum was prepared were found to be the cause of death, and in 2, hemolytic streptococci caused death. Also in these cases improvement could not be expected. In all cases in

which specific agglutination was obtained, marked improvement followed injection of the serum, and in no case were good effects noted at a time when agglutination tests were negative.

The influenza bacilli found in the sputum in 2 cases might be regarded as unimportant invaders since both patients showed marked improvement following injections of the serum. The cases were of course too few from which to draw sweeping conclusions, but since they were controlled by immunologic studies the results indicate anew that diplostreptococci, closely related to pneumococci on the one hand and hemolytic streptococci on the other, bear important etiologic relationship to influenza and to influenzal pneumonia, especially early in the attack, and that the injection of properly prepared hyperimmune serums may prove curative in those cases due to organisms immunologically identical to those used in the preparation of the serum, quite as has been found in the case of type pneumococcus infections in lobar pneumonia.

The changes which occurred in bacterial flora as measured by cultural and immunologic tests during the course of the disease, emphasize the complexity of the problem and the need for their consideration in the development of specific methods of prevention and treatment of influenza and its complications. The question whether or not these changes are the result of superimposed infection or modifications, mutations perhaps of the organisms present in the beginning of the attack, will be considered in subsequent reports.

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## PULMONARY SUPPURATION\*

C. A. HEDBLÖM\*

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Pulmonary suppuration is a comprehensive term. Anatomically the bronchi or the parenchyma alone may be primarily involved, or the pulmonary infection may arise by perforative extension from an adjacent structure. Pathologic subdivisions of the term are abscess, gangrene, bronchiectasis, and purulent bronchitis.

Gangrene of the lung is largely a pathologic distinction. Typical cases of massive gangrene may be recognizable clinically but all intermediate gradations of abscess and gangrene occur. Each may supervene on the other. When we diagnose pulmonary gangrene and when we get it for treatment it is almost always accompanied by suppuration; it is abscess and gangrene.

On a therapeutic basis suppurating tuberculous cavities, purulent bronchitis, and diffuse bronchiectasis are excluded. A localized bronchiectatic process on the other hand often cannot be differentiated clinically or by x-ray from abscess. The distinction may be difficult to make at operation also. For the purposes of this discussion, therefore, localized bronchiectasis is included with abscess and gangrene.

### HISTORICAL

Hippocrates taught that a pulmonary abscess that had burst into the pleural cavity could be healed by draining the latter. Schenk, in 1584, is credited with a case in which he promoted spontaneous rupture by fomentations, and so forth. Even though this may have been an instance of empyema necessitatis it constitutes evidence that the occurrence of pulmonary suppuration was recognized at this date. Baglivi, 1696, is said to have been first to establish drainage by intercostal incision. Barry, in 1726, reported two cured cases and one fatal case following incision for drainage. Campardon, in 1759, described in

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detail the case of a patient with typical symptoms cured by draining an abscess that pointed into the chest wall. Sharpe, in 1769, and Pouteau, in 1793, reported operative recoveries. In 1793 Gumprecht published a remarkable monograph on the diagnosis, prognosis, and treatment. He states that before surgical treatment should be instituted it is necessary to determine the presence and seat of pus and the condition of the pleura as to adhesions. He cites several cases in which operation was successfully done, discards one as probably being empyema, and details the necropsy findings in one insufficiently drained, fatal case.

Further development in the surgery of pulmonary suppuration was uncertain and slow. After another hundred years Garré was able to collect from the literature only 122 cases of abscess in which operation was done, and many of these he considered of doubtful diagnosis. The literature from 1800 to 1880 consists chiefly of individual reports of spontaneous cures and of postmortem findings. Huntington, in 1876, reported 32 cases from the Massachusetts General Hospital; these had been observed during the preceding eighteen years. None of the patients was operated on. Most of the operations in this period were trocar puncture, or incision of the abscess pointing into the chest wall. Intercostal incision and pneumotomy were performed by Faye, Bell, Jaymes, Zang, Hawthorn, Sutton, Stokes, Dickson, and others.

The uncertain results of thoracotomy stimulated search for other methods. Green, in 1860, attempted to catheterize the air passages to promote nature's method of drainage. He states that at various clinics injection of antiseptics into the bronchi have been frequently attempted. Mosler, Koch, and Frankel, following animal experimentation, attempted sterilization of the lung parenchyma by the injection of carbolic acid, tincture of iodine, salicylic acid, and so forth. Mosler and others also used carbolic acid irrigation of abscess cavities drained by thoracotomy.

The basis for the further development of the surgery of the lung was furnished by the results of animal experimentation, notably of Jaszko, Gluck, Schmid, and Biondi. Of especial influence on thoracic surgery was the demonstration by Gluck and others that animals can survive resection of the lung. The prevailing conception that the brain, heart, and lungs—the tripod of life—are beyond the reach of surgical intervention was modified by the experimental proof that one

lung, like other paired organs, is capable of functioning for both. Of the early clinical contributions perhaps the most important are those of Christian Fenger in 1881, and of Bull in 1881—1884. Fenger reported 5 cases from the literature and one case in which he had operated. Bull in 1882 reported 19 cases, 14 of which he considered beyond question as to the pathology involved. Runeberg, in 1887 published a critical study of 7 cases of abscess, 10 of gangrene, 2 of echinococcus, and 6 of bronchiectasis. In an important monograph

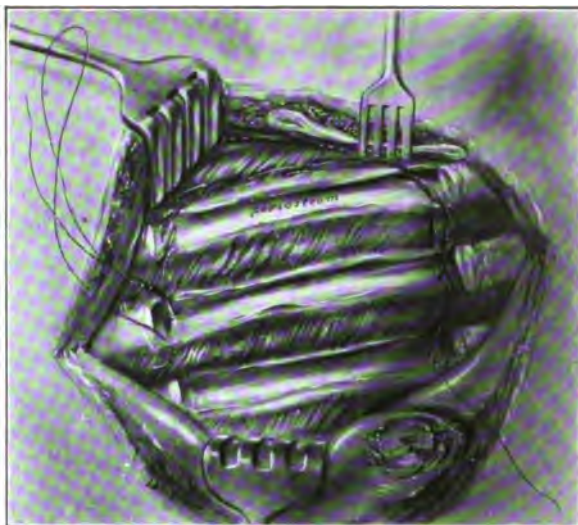


FIG. 374.—First-stage operation, showing suture of lung to intercostal bundles and parietal pleura.

published in 1897 Tuffier reported a series of 216 thoracic cases in which operation had been done; the series included 36 of caverns, 49 of abscess, 45 of bronchiectasis and, 11 of foreign body abscess.

The accumulation of literature since then has been relatively rapid. In 1903, Garré was able to add 278 cases, and in 1912 he collected 182 cases, making nearly 600 in all. The important series of personal cases of Körte, Lenhartz, and Külbs and several series of collected cases will be referred to in connection with operative results.

Up to 1919, 70 patients have been operated at the Mayo Clinic for pulmonary suppuration. The combined mortality from all causes including bronchiectasis is 33.3 per cent. The present study is concerned chiefly with 54 cases in which operation has been done since

1910. Eight of these cases were operated on by Beckman, 9 by Judd, and 17 each by Robinson and myself. There are included also 2 cases that progressed to a spontaneous cure and 24 necropsy cases. In 17 of the 24 necropsy cases abscess occurred as a postoperative complication; in 16 the abscesses were multiple. In 7 instances the patients were either moribund at admission or the condition was not recognized clinically. The grouping of these 80 cases may be seen in Tables 1 and 2.

TABLE 1

Patients operated on for pulmonary suppuration:	
Acute abscess.....	30
Chronic abscess.....	17
Bronchiectasis.....	7
Spontaneous recovery.....	2
Abscesses found at postmortem:	
Surgical cases.....	17
Medical cases.....	7
	<hr/> 80

TABLE 2.—AGE AND OCCUPATION

Under 10 years.....	2	Farmer.....	33
From 11-20 years.....	3	Laborer.....	20
From 21-30 years.....	17	Business man.....	15
From 31-40 years.....	22	Physician.....	3
From 41-50 years.....	20	Congressman.....	1
From 51-60 years.....	11	Student.....	1
From 61 years.....	5	Druggist.....	1
		Bartender.....	1
Males 65, females 15		None.....	5

### ETIOLOGY

Primary suppuration of the lung is probably rare. It develops on a preceding inflammatory process or the infection is carried to the lung tissue through the bronchus, the blood stream, or by direct extension. Of the inflammatory lesions, pneumonia appears to be the most common. At the Massachusetts General Hospital Lord found pneumonia to be etiologic in 14 of 50 cases of abscess and in 8 of 50 cases of gangrene. Microscopic abscesses were found in 10 of 85 fatal cases of bronchopneumonia. Bronchopneumonia following influenza is often complicated by abscess, often multiple and usually subpleural. Oberndorfer in a series of postmortem studies reports the frequent occurrence of infarct-like areas near the pleural surface

of the lung. In the later stages these areas either become gangrenous or break down into abscess cavities. Oberndorfer also observed frequent purulent bronchitis, and bronchiolitis in many instances with cylindrical bronchiectasis. Many other writers report similar observations.

The frequency of necropsy findings of abscess associated with pulmonary suppuration varies according to different observers. Bell reports 30 necropsies, Stone 55, and Ely 39 without pulmonary abscess. Hunt in 30 examinations found abscesses in 2, Wegelin in 68 found mul-

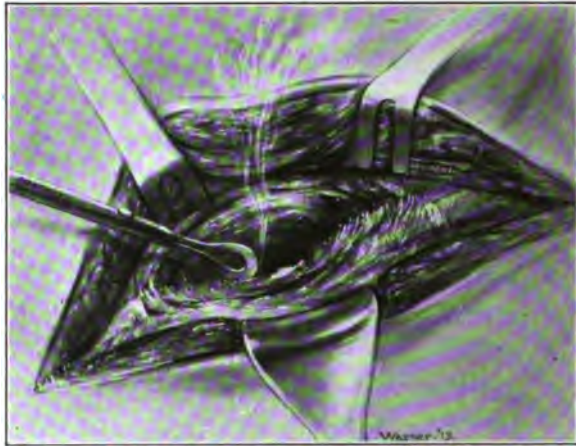


FIG. 375.—Second-stage operation, showing burning of funnel-shaped opening through the lung tissue down to the abscess.

tiple small abscesses in 12. Coutant reports one. Opie in 200 necropsies found "suppuration" in more than 25 per cent. At the Mayo Clinic in a few more than 100 prolonged influenzal pneumonia cases examined, abscesses were found in 3. Many cases have been observed clinically in which symptoms of abscess were present. In one instance the patient expectorated in twenty-four hours eighteen ounces of thick purulent sputum. This patient made a complete recovery after drainage of the empyema, probably following rupture of the abscess into the pleural cavity. In the available literature I have found no mention of operation for acute abscess complicating influenzal pneumonia.

Deaver reports 13 cases of interlobar empyema in which operation was done; in many rupture into the lung had occurred. Weil had a series of 7 cases of gangrene of the lung following influenza. Pneu-

mothorax following rupture of subpleural abscess is reported by the Influenza Committee of the British Armies in France, by Weber, and by others. Within the past few months I have frequently observed empyema with bronchial fistulæ, presumably from small superficially situated abscesses.

Aspiration of infected material appears to be a more frequent cause of abscess than is generally recognized. Of considerable interest



FIG. 376 (216141) Dec. 8, 1917.—(Acute abscess.) Roentgénogram made ten days before operation.

and importance are the apparently relatively frequent lung abscesses following tonsillectomy. A number of such cases have been reported recently. Claytor reports 4 cases with recovery. Frank found 5 in the records of the Michael Reese Hospital, Chicago, for the last ten years. In reply to a questionnaire sent to 50 internists, surgeons, and nose and throat specialists he learned of 15 others. Of these Warthin reported three postmortems in students. Bevan of the Presbyterian Hospital, Chicago, writes "we have certainly had from

ten to a dozen abscesses in the last two or three years, many fatal following tonsillectomy." Manges reports 6 admitted to the Mt. Sinai Hospital within six months. Scudder mentions several. Tewksbury reports having seen 15 in one year following nose and throat operations. Bassin has collected 19 cases with a 75 per cent mortality. Most of these tonsillectomies were done under general anesthesia. Five cases in my series of 56 followed tonsillectomy under general



FIG. 377.—Case shown in Figure 376. Dec. 18, 1917. Roentgenogram made ten days later, before operation. Note marked increase in density of shadow.

anesthesia done elsewhere. Coakley believes such cases are due to aspiration of blood infected by the cheesy or milky bacteria-laden secretions squeezed out at operation, and that the infection is not embolic. The fact that following approximately 16,275 tonsillectomies performed at the Mayo Clinic from January, 1910 to January, 1919, there has not been a single known instance of abscess of the lung, is evidence in support of this contention.

Inhalation of infective material from the mouth or of a tooth during extraction is not an uncommon cause (Quinke, Schulz and Külbs) Six such cases are herein recorded.

Aspiration of particles of food, mucous flakes, epithelial shreds and so forth, probably occurs with sudden inspiration as in laughter, hurried eating, narcosis, stupor, deep sleep, and following disturbances of pharyngeal and laryngeal innervation. There was a probability of



FIG. 378 (216141).—Jan. 21, 1918. (Acute abscess.) Case shown in Figures 376 and 377. Roentgenogram made three weeks after operation.

foreign body abscess in 12 of 41 cases reported by Külbs. Aspiration of fairly large organic bodies unknown to the patient should be borne in mind as a possibility in cases of suspected foreign body abscess in which the x-ray shows no foreign body.

In a series of 40 cases seen at the Mayo Clinic a foreign body in the bronchus cast no shadow by x-ray in 23. Twelve were peanut kernels, 6 kernels of corn. In 14 instances the foreign material had



been present more than a month and in 7 more than two years. In one instance a tack had been in the bronchus for ten years and had not caused symptoms. In another instance a tack had been present unsuspected three and one-half years. The patient was sent to a tuberculosis sanitarium where x-ray disclosed the foreign body. Such an aspiration infection is possibly the etiologic factor in many cases of pulmonary abscess and bronchiectasis in which no definite cause can be ascertained.



FIG. 379.—Case shown in Figures 376, 377, and 378. April 11, 1918. Roentgenogram made three and one-half months after operation. No symptoms, no sinus. Patient gained 50 pounds in weight.

The frequency of abscess from prolonged retention of bullets, shrapnel, and so forth, is of considerable interest at this time. Various authors, Dean, Elliott, Archibald, Gask and Wilkinson, Eggers and Hale White express the opinion that abscesses following war injuries were very rare. Bennett, Gregoire, Haim and others, however, report cases of abscess. Duval believes retained foreign bodies are always

potential sources of infection. Turner, after four years' experience writes that in operating in these cases he has often found localized collections of pus in connection with the foreign body. He believes many cases of infected hemothorax and empyema have arisen by perforation of such an abscess.

The etiologic factors in the 56 cases of primary suppuration herein reported are noted in Tables 3 and 4. In Table 3 it may be seen that

TABLE 3.—ETIOLOGIC FACTORS

Primary abscess	Cases	Acute abscess	Chronic abscess	Bronchiectasia
<b>Primary abscess:</b>				
Pneumonia.....	13	7	4	2
Tonsillectomy.....	5	3	2	
Empyema.....	4		2	2
Extraction of teeth.....	6	5	1	
Grippe.....	2		1	1
Foreign body.....	1		1	
Dust.....	1	1		
Trauma*.....	1	1		
Hepatic abscess.....	1		1	
Subdiaphragmatic abscess...	1	1		
<b>Abscess after operations:</b>				
Cancer of stomach.....	1	1		
Gastric ulcer.....	2	2		
Duodenal ulcer.....	1	1		
Appendicitis.....	1		1	
Questionable.....	14	8	4	2
<b>Primary abscess not operated on:</b>				
Tonsillectomy.....	1	1		
Pneumonia.....	1		1	
	56	31	18	7

\* Followed by pneumonia.

in 14 cases (25 per cent) the abscess developed on a preceding inflammatory lung condition; in 14 (25 per cent) there was presumptive evidence of the infection having been carried to the lung by foreign material (detritus during tonsillectomy, teeth, dust, and other foreign bodies. In at least 10 (18 per cent) there was a possibility of infection by direct extension from an adjacent inflammatory process (empyema, peptic ulcer, abscess).

Preceding disease incidence in the 24 cases in which abscess was found at postmortem is noted in Table 4. In 6 (25 per cent) there was a preceding inflammatory process in close proximity to the lung. In 8 (33.3 per cent) operation was performed for malignant disease. The lesion was probably metastatic in 6 (25 per cent) of the infected cases; there was a preceding pneumonia in one case of malignant disease. The lung infection probably occurred by direct extension in one, and by metastasis in 6 (25 per cent). Sixteen (66.6 per cent) of the whole group were cases of multiple abscesses; there was one of bilateral gangrene.

TABLE 4.—NECROPSY CASES (OPERATION)

<b>Inflammatory lesions:</b>	
Subdiaphragmatic abscess.....	2
Gastric ulcer.....	1
Duodenal ulcer.....	2
Infected kidney.....	2
Tube ovarian abscess.....	1
Exophthalmic goiter.....	1
Empyema.....	1
<b>Malignant disease of</b>	
Lip.....	1
Esophagus.....	1
Stomach.....	2
Sigmoid.....	1
Rectum.....	1
Kidney.....	1
Uterus.....	1
<b>No operation:</b>	
Otitis media*.....	1
Facial cellulitis.....	1
Endocarditis.....	1
Puerperal infection.....	1
Indeterminate.....	2
	<hr/>
	24

\* Operation elsewhere.

### SYMPTOMATOLOGY

The most suggestive single symptom of pulmonary suppuration is a chronic productive cough. Because the abscess has usually burst into a bronchus at the time the patient is first observed the sputum is frankly purulent. If the perforation has not yet occurred or if the drainage thus established is inadequate the sputum may be mucoid or mucopurulent and inconsiderable in amount. Sometimes it is

watery and brownish from admixture of blood. Associated symptoms in varying number and degree are chills, fever, night sweats, hemoptysis, pleuritic pains, weakness, and rapid, often excessive loss of weight. Some of the characterizing features of the expectoration in the 56 cases are shown in Table 5.

TABLE 5.—EXPECTORATION

<b>Onset:</b>	
Paroxysmal.....	16
Gradual.....	25
Not stated.....	15
<b>Amount:</b>	
Excessive.....	20
Moderate.....	17
None.....	1
Not stated.....	18
<b>Character:</b>	
Foul.....	35
Sweet.....	1
No Odor.....	2
Not Stated.....	18
<b>Expectoration:</b>	
Periodic.....	24
Not stated.....	32
Influenced by gravity.....	8
<b>Elastic tissue</b>	
Found.....	2
Not found.....	12
Not stated.....	42
<b>Tuberculosis bacilli:</b>	
Found.....	1
Not found.....	41
Not stated.....	14

A sudden onset of sputum during a paroxysmal coughing spell is usually considered as most characteristic of abscess. In this series the onset was gradual in at least half the cases, probably this was also true in most of the 15 cases in which the mode of onset was not stated. The amount of sputum varied from a few ounces to a quart in twenty-four hours. The odor was characteristically foul, notably so in some of the cases of probable inhalation abscess. Repeated examinations were made for tuberculosis bacilli in 42 cases. The one case in which bacilli were found was probably one of associated tuberculosis and abscess. The onset of sputum in this case was sudden and the

amount excessive. A syndrome suggestive of tuberculosis may be seen in Table 6.

A leukocytosis, when present, is of value as an indication of suppuration, but a normal count does not signify its absence (Table 7).

TABLE 6.—SYMPTOMS SUGGESTIVE OF PULMONARY TUBERCULOSIS

Fever	Loss of weight	Hemoptysis	Night sweats	Pleuritic pains
Present..... 30	10-20 pounds 17	Present..... 18	Present..... 14	Present..... 30
Absent..... 5	20-40 pounds 11			Absent..... 4
Not stated.... 21	40-60 pounds 3			Not stated.. 22
	Not stated.. 25			

TABLE 7.—LEUKOCYTOSIS

None.....	9 cases
11,000-15,000.....	6 cases
15,000-30,000.....	20 cases
Not stated.....	21 cases

The physical signs of pulmonary suppuration vary and their significance is uncertain. Associated thickened pleura, pleurisy with effusion, pneumonitis surrounding the abscesses, sequestrum blocking the bronchus of the affected area, varying amounts of pus in the abscess cavity and the distance of the abscess from the periphery of the lung are some of the variable factors which lead to uncertainty as to the presence, location, and character of the lesion. Dullness to percussion seems to be the most reliable sign. It was present in 92 per cent of these cases (Table 8).

TABLE 8.—PHYSICAL SIGNS

Dullness to percussion.....	36 cases
Associated bronchial breathing.....	8 cases
Distant breathing.....	17 cases
Negative physical examination.....	2 cases
No record.....	18 cases
	56

## DIAGNOSIS

The diagnosis rests largely on the presence of cough with sputum, on the clinical signs and symptoms of infection, and on the x-ray. A history of previous inflammatory disease of the lungs or of possible aspiration of infected material is of decided value. X-ray examination

is very useful, especially in the differential diagnosis, and in the localization of the process. The x-ray findings studied in the light of the clinical aspects of the case will usually lead to a correct diagnosis. In attempting to evaluate the comparative reliability of the x-ray and clinical methods of diagnosis it must be borne in mind that the clinical diagnosis is usually made with the aid of the x-ray while the x-ray



FIG. 380 (228271).—May 28, 1918. (Acute abscess.) Roentgenogram made just before operation.

diagnosis is apt to be independent of the clinical history and findings. In some cases operation proves both methods fallacious, and, unfortunately, the postmortem examination at times also reveals the failure of the operation.

Twenty-four of these 47 cases were diagnosed alike clinically and by the x-ray. In 8 additional cases, in 4 of which the x-ray had not been used, the clinical diagnosis of abscess was proved correct at operation. In 8 other cases diagnoses were made clinically and by x-ray but no abscess was found at operation. In 5 of these 8 the

abscess was found postmortem. In 5 cases proved at operation the clinical and x-ray diagnosis was either empyema or subdiaphragmatic abscess. One case diagnosed gangrene clinically and pleuritis by the x-ray proved to be abscess. A diagnosis of bronchiectasis was made in only one case both by x-ray and clinically. In one questionable case the clinical diagnosis lay between abscess and bronchiectasis. In another case the x-ray diagnosis was "dense" infiltration.



FIG. 381.—Case shown in Figure 380. Sept. 6, 1918. Roentgenogram made three and one-half months after operation. Slight residual cough. No sinus. Gain in weight about 50 pounds.

In the differential diagnosis tuberculosis, encapsulated empyema, generalized bronchiectasis, fibrosis, perforation of adjacent structures by the abscess, and malignant disease are chiefly to be considered. Of these tuberculosis is the most common and the most important. Tuberculosis may be mistaken for suppurative disease but the error of mistaking a purulent lesion for tuberculosis is more frequent. Furthermore the association of the two conditions is undoubtedly more frequent than is generally recognized. In 17 instances in this

series of 56 cases there was apparent evidence of a primary or of an associated tuberculous lesion. A more or less characteristic syndrome of tuberculosis was present in all of these 17 cases. Cough with sputum, hemoptysis, fever, night sweats, and loss of weight in varying combinations was present in all. A definite diagnosis of associated tuberculosis was made in 5. Tuberculosis bacilli were found in the sputum in one instance only. Seven of the 17 patients died, 9 improved or were entirely relieved of their symptoms by operation. A postmortem examination was made in 6 of the 7 fatal cases. In 2 a tuberculous process in addition to the abscess was found, in the other 4 a suppurative lesion, but no tuberculosis. Of the 9 patients who recovered eight were practically cured by operation and were well at the time of the last report, three to fourteen months. The detailed findings in these 17 cases are recorded in Table 9.

An encapsulated or interlobar empyema, probably as a rule secondary to the rupture of a lung abscess, may present a confusing picture. The early history is likely to suggest abscess, the presenting symptoms and physical findings being those of empyema. The sequence of symptoms is of some significance. Trousseau stated that an abscess will burst through into the bronchus in from twenty to twenty-five days, and that empyema will break into the lung not earlier than the fortieth day. In the presence of a diffuse shadow shown by the x-ray it may be impossible to decide which perforation has occurred. If an encapsulated empyema is found at operation a funnel shaped depression in the lung may mark the site of an old abscess or there may be an open fistula. The presence of dense pleural adhesions in such cases makes a correct preoperative diagnosis of less practical importance than if they were absent.

A circumscribed bronchiectasis may be difficult to distinguish from abscess. From the fact that either condition predisposes to and often is the cause of the other it follows that the two are often associated. In such cases, if a dense circumscribed shadow only is shown by the x-ray the diagnosis must be made on the history and symptoms. In the series of 7 cases herein reported the pre-operative diagnosis was correct in only 2.

Malignant disease of the lung is comparatively rare yet not so rare but that it must be considered in a differential diagnosis. In three cases not included in this series exploration was done for lung abscess. One was a case of central growth, probably sarcoma; the patient died



TABLE 9.—SEVENTEEN CASES SUGGESTIVE OF TUBERCULOSIS INFECTION

No.	Cough	Sputum	Hemoptysis	Fever	Night sweats	Loss of weight	Physical findings	X-ray findings	Operative findings	Subsequent history
36004	10 yrs.	Excessive 10 yrs.	+	-	-	0	Localized flatness to percussion	Central abscess	Abscess	Five months after operation repeated sputum examinations and tuberculin tests were negative. *Abscess. No tuberculosis. Tuberculosis bacilli found in the sputum.
36479	11 yrs.	11 yrs.	Slight	+	0	+	Tuberculosis left lung abscess right base	.....	Abscess	
56674	10 yrs.	10 yrs. Excessive	+	+	+	+	Dullness, harsh breathing, friction rub, increased vocal resonance of right base	Abscess. Mass in mediastinum	Aspiration	
57500	6 mos.	Excessive foul	-	0	-	+	Dullness, coarse râles over right middle lobe	Abscess middle right lobe	Abscess	*Abscess. pulmonary embolus, empyema, old tuberculosis. Died 5 months after operation. No necropsy.
74081	8 mos.	Excessive foul	+	+	-	+	Dullness and râles over left base	Dense shadow in left base	Abscess	*Abscess. left empyema, left bronchiectasis, fibropurulent pericarditis. No tuberculosis.
130276	6 mos.	6 mos. foul	+	+	0	+	Râles right apex and left base	Probably old abscess in left base	First stage operation	Reported complete recovery 3 months after operation. Reported recovery 4 months after operation.
169070	6½ mos.	+	Slight	0	-	Slight	No signs	Tuberculosis of upper left lobe	Multilobar abscess	
194204	6 mos.	+	+	+	-	+	Questionable signs of cavity in right upper lobe	Dense consolidation right upper lobe.	Abscess	*Abscess. bronchopneumonia. Emphysema. No tuberculosis.
195207	3 yrs.	Excessive	+	+	-	+	Slight dullness, right back	Probable central abscess base upper right lobe	Abscess	No clinical evidence of tuberculosis 18 months later.
202460	8 mos.	+	+	+	-	+	Râles, distant breathing in right base	Thickened pleura right base. Fluid.	Bronchiectasis	*Abscess right lung. Empyema. Healed and active, tuberculosis of both lungs. Recovery. No recurrence of symptoms 14 months after operation.
202937	2 mos.	+	Profuse	+	+	+	Impaired resonance right apex. Râles left base. Râles right base.	Old abscess? middle right lobe	Abscess	No recurrence of symptoms 18 months after operation. No symptoms 10 months after operation. Gained 50 pounds in weight.
215058	9 mos.	Excessive	Slight	+	0	+	Dullness left lung. Increased fremitus right apex. Fremitus complete left base	Tuberculosis upper right lobe. Thickened pleura and fluid in left base	Abscess right base	No recurrence of symptoms.
218028	2 yrs.	+	+	+	+	+	Complete dullness of right base. Harsh breath sounds right apex. Dullness and absent breath sounds at right base.	Thickened pleura right base. Fluid. Tuberculosis left lung. Unresolved pneumothorax (?) right lung	Bronchiectasis	
228271	16 mos.	16 mos.	Profuse	+	-	+	Dullness and râles left base	Probable abscess lower left lung	Abscess right lung	
235040	7 mos.	7 mos. Foul	Profuse	+	+	+	Râles right upper lobe. Dullness lower lobe. Lower right flat	Abscess? right lower lung. Fluid thickening. Fluid lower right	Abscess	
236782	8 mos.	8 mos.	+	+	+	+			Abscess	No recurrence of symptoms.
239504	1 yr.	11 mos.	+	+	+	+			Abscess	*Multilobar abscesses, empyema, pericarditis. No tuberculosis.

\* Necropsy.

a few months later at home and, unfortunately, no postmortem was obtained. A second case was one of carcinoma, apparently primary, in the lung with associated bronchiectasis, a third was found at post-mortem to be one of carcinoma of the left adrenal with metastasis to the left lung.



FIG. 382 (236782).—June 27, 1918. (Acute abscess.) Roentgenogram made just before operation.

Another probably rare condition simulating abscess is localized fibrosis of the lung. One such case was explored repeatedly for abscess but no definite focus was found. The patient is at present improving slowly, approximately two years following the onset of the symptoms.

#### TREATMENT

The treatment of pulmonary suppuration is drainage. The anatomic relations of lung parenchyma, bronchi, and trachea, are such as to provide spontaneous evacuation once the abscess has opened into a bronchus. During coughing the lungs are compressed by the

wall of the chest and by the diaphragm; this further aids in expelling the pus. The patients often discover that certain positions favor expectoration and so unconsciously make use of gravity to help empty the cavity. That spontaneous cures result in this manner is to be expected. Probably a great many cases of small abscesses in which the symptoms are mild are never recognized. On the other hand



FIG. 383.—Case shown in Figure 382. Dec. 30, 1918. Roentgenogram made six months after operation. Slight residual cough and sputum. Marked gain in weight.

a not inconsiderable number of unquestioned cases of spontaneous cures are recorded. Even abscesses perforating from the liver have been cured by promoting gravity drainage (McKechnie). Acute cases of a mild type, according to many writers of experience, may therefore be treated expectantly for a few weeks in the hope that drainage through a bronchus may effect a cure. Even in such cases it must be recognized that the presence of pus in the bronchial tree is a constant menace to other portions of the lung.

The mortality following expectant treatment in general was early found to be very high. Lenhartz, 1905, quoting statistics from three large municipal hospitals in Berlin, Verneuil, Picot, Kissling, Baron and others reported it at from 60 to 100 per cent.

The operative mortality for gangrene in relatively large series of cases collected by Garrè and by Picot was 29.3 per cent and 29.5 per



FIG. 384 (213924).—Dec. 19, 1917. (Chronic abscess.) Roentgenogram made just before operation.

cent respectively. Lenhartz, 1907, had a 37.6 per cent mortality in 85 cases. Sauerbruch found the mortality following a drainage operation for bronchiectasis to be 35 per cent in 123 collected cases.

Both mortality and morbidity are greatly reduced by early operation. This is strikingly shown by the reports of Freyhan, Külbs, Schulz, Scudder, and especially by Eisendrath. In a series of 53 acute and 40 chronic postpneumonic abscesses, Eisendrath found the operative mortality to be 11.3 per cent and 35 per cent respectively.

The mortality in 30 acute cases herein reported was 33.3 per cent; in 17 chronic cases it was 47 per cent. The mortality following operation for abscess in several series of cases is indicated in Table 10.

TABLE 10.—OPERATIVE MORTALITY

Author	Year	Cases	Source	Mortality
Garrè.....	1903	400	Collected	25.0
Garrè.....	1912	182	Collected	18.6
Tilton.....	1907	20	Collected	50.0
Kissling.....	1906	120	Lenhartz	40.8
Whittemore.....	1915	27	Mass. Gen. Hosp.	25.0
Körte.....	1908	37	Personal	40.0
Kulbs.....	1913	24	Personal	25.0
Hedblom.....	1919	54	Mayo Clinic	33.3
Hedblom.....	1919	17	Personal	23.5



FIG. 385.—Case shown in Figure 384. Jan. 18, 1918. Roentgenogram made one month after operation. Report of improvement six months after operation. Fistula.

The surgical treatment aims at facilitating drainage and healing of the abscess cavity either by carrying nature's method one step farther—collapsing the lung walls—or by drainage from the outside, and if necessary in chronic cases by mobilizing the chest wall to secure collapse of the cavity and healing. The radical excision has been reserved for extreme cases of destruction of the lung substance and for bronchiectasis. The mortality following this radical procedure has been uniformly high. In chronic cases in which the abscess wall is rigid collapse may be attained by rib resection. Radical rib resection operation was performed by Macewen in 1906. Perthes recommends a two-stage operation, mobilization of the chest wall being deferred until the patient's condition warrants it. Tuffier in 1914, without opening the abscess, secured partial collapse of the cavity by separating the parietal pleura from the chest wall and inserting masses of fat. He has reported two cures by this method. Forlanini has adapted his artificial pneumothorax therapy for tuberculous cavities to those of pyogenic origin. In 1910 he reported a cure in a case of six years' duration. The treatment lasted twenty-five months. Izar reports one successful and one unsuccessful case. He refers to three others, among them one by Volhard, in which improvement followed the establishment of a complete pneumothorax, but the patient died in one month of empyema. Tewksbury has reported 10 acute and 2 chronic cases. Eight patients were cured, 2 were temporarily improved, and 2 died, one of empyema. Artificial pneumothorax seems rational and promising in cases of deep seated abscess. It had been used elsewhere in 2 cases herein reported. In one there seems to have been some benefit, since hemoptysis was temporarily checked. In another case an extensive cellulitis of the whole chest wall resulted. The patient presented himself a year later with a huge chronic abscess which was drained. Two months after the operation he died of hemorrhage.

Robinson used pneumothorax therapy in one case of postoperative abscess with brilliant result. In another case of central abscess following gangrene, appendicitis, and subdiaphragmatic abscess, the same treatment was attempted without result. In acute central abscess this form of treatment is certainly the safest and seems promising. The presence of pleural adhesions, however, in approximately 50 per cent of cases will always limit the applicability of the method. Partial collapse of the lung has been effected by Bruns and Sauerbruch by ligating the major pulmonary arterial branches.

Thoracotomy with rib resection and pneumonotomy is the operation most extensively practiced and will probably remain for most cases the operation of choice.

The indication for operation is the presence of a purulent localized focus and marked characteristic constitutional symptoms that are not on the mend. The question of whether the process is acute or chronic, single or multilobar will modify materially the operative procedure and the prognosis, but operation is to be advised on principle. Localized bronchiectatic processes would best be placed in a separate group were it possible always to diagnose them as such. Bearing in mind the difficulty in diagnosis in this group of cases and the fact that localized abscess and gangrene may supervene on bronchiectatic foci, probably more harm than good would result from attempting to differentiate borderline cases. The decision as to operative interference in the desperately sick may be very difficult. Operation in such cases as a last resort will increase mortality statistics but it will save lives. The patient is entitled to his chance.

#### ANESTHESIA

General anesthesia is favored more or less by many continental surgeons (Tuffier, Lenhartz, Kissling, Körte, Picot). Küttner, Quincke and Garrè, Külbs, Murphy and others prefer, whenever possible, local anesthesia. In my hands local and nerve trunk anesthetics have been very satisfactory. The safety with which a two-stage operation may be done by this method makes it possible to extend the operative indication to desperate cases in which general anesthesia would be prohibitive.

#### OPERATION

The incision is made over the effected area as localized by physical findings and especially by the x-ray. If the focus is in a lower lobe a lateral or postero-lateral incision is usually best; if in the upper lobe anterior incision gives the best exposure. The presence of the scapula and thick back muscles limits the area that can be exposed high posteriorly. In two recent cases in which the abscess lay posteriorly and high, good exposure was obtained by resecting the angle of the scapula. An incision larger than seems necessary should be made. As has been well said—"better two ribs too many than one too few." One is continually impressed with the rapidity with which a wound in the

chest wall heals. If the incision is not ample it will close to a small sinus before the cavity in the lung has become obliterated.

Subperiosteal resection of 4 inches of two or three ribs suffices for exploration. The further procedure depends on the presence or absence of adhesions of the lung to the parietal pleura. A thickened greyish opaque pleura indicates the presence of adhesions. In some cases without adhesions, the movement of the lung can be seen through the pleura. In other cases there may be adhesions in one part of the exposed area and not in another. In still other cases a small incision through the pleura may be necessary to settle the question. A safe procedure recommended by many thoracic surgeons, and one I have followed, is in case of doubt to proceed as though adhesions were not present.

If adhesions are not present or if they are doubtful, or only partial, as occurs in about half the cases, the pleural cavity is walled off by suturing the lung to the pleura and intercostal muscles with continuous catgut stitches after the method of Péan and Roux. Suturing through the intercostal tissue prevents tearing of the pleura and the added difficulties due to partial pneumothorax and retraction of the lung. Körte, in six instances, found it necessary to seize the lung with forceps and drag it out into the wound before he could complete the suture. In one case, because of violent coughing I encountered a little difficulty but the lung did not collapse. When the lung is sutured securely the circumscribed pleura may be opened at once without danger of lung collapse. But there is still danger of leakage along the suture line which also may tear. The empyema that may result is a serious and often fatal complication. Unless immediate drainage is indicated it is therefore safer to wait a few days before attempting to drain the abscess. Other or supplementary methods of protecting the pleura by provoking adhesions are iodoform gauze packs, chemical irritants, zinc chlorid paste, tincture of iodine, cautery, and electrolysis. In my hands simple suture through the intercostal bundles has been sufficient.

The most important and often most difficult part of the operation is finding and draining the focus. Garré and Quincke write, "It is difficult, often very difficult, to find the focus correctly diagnosed, when it lies low down in the lung towards the hilum or base of the lung." Tuffier (1914) mentions a case in which nine punctures with a large trocar failed to penetrate a cavity as large as a fist, which



contained 500 c.c. of pus. Tuffier (1910) has done extensive rib resections to make possible transpleural palpation of the lung.

The wide open thoracotomy recommended by some French surgeons is open to the serious objections of pneumothorax, danger of infection and difficulty in finding the lesions. Picot describes a method for holding the lobe in the wound by transfixing sutures for both exploration and incision. Robinson lays bare the adherent visceral pleura by incising the posterior rib sheath, and by establishing with the finger a plane of cleavage in the thickened pleura.

Exploratory puncture with an aspirating needle seems the safest and most accurate method of localizing the abscess. It is important in this connection to remember that the pus is most apt to lie in the parenchyma. In 30 postmortem cases at the Massachusetts General Hospital the abscess was at or near the periphery in 28 (Lord, 1909). The danger of piercing a large vessel by directing the needle deeply or by using a very large one must be recognized. In several cases in my series hemoptysis occurred, in two with temporary but alarming dyspnea and cyanosis.

If pus is aspirated, cautery incision along the tract of the needle, burning a funnel shaped path, furnishes adequate exposure for the search for secondary pockets after the cavity is reached, and for drainage. If the cautery is kept at a dull red heat good hemostasis is also secured. Occasionally no pus but only air is aspirated. Willy Meyer considers this significant of the entry into the abscess cavity provided the aspirating apparatus is tight. In my experience air has been aspirated apparently from the bronchi.

If no pus is aspirated, burrowing into the dense area with a blunt instrument or with the finger is recommended. In one such case, after repeated negative aspirations I incised the dense area with the cautery. Even though no pus was encountered the patient made a strikingly rapid and complete recovery. In a similar case no marked improvement followed two cauterizations. The patient died suddenly after an acute hemorrhage three weeks after the operation. Necropsy showed an aneurysmal vessel burst into the cavity. The cautery had failed to reach the abscess by less than half an inch.

Garré and Quincke strongly recommend careful investigation of the cavity for secondary cavities. Körte inspects the cavity with a cystoscope.

A gauze pack is probably the best safeguard against hemorrhage

TABLE 11.—OPERATIVE FINDINGS IN THIRTY CASES OF ACUTE ABSCESS

No.	Anesthetic	Location of abscess	Pleural adhesions	Primary drainage	Pleural cavity opened	Pus found	Hemorrhage	Cavity	End results	Necropsy findings
39325	Ether	Right lower	Yes	Yes	?	Yes	No	Single	Recovered in 2 months	Large abscess, tuberculosis, gangrene most of lung. Abscess, empyema, bronchiectasis, pericarditis. None.
44307	Ether	Right lower	Yes	Yes	?	Yes	Slight	Single	Recovered in 16 months	
45690	Ether	Right lower	Yes	Yes	?	Yes	No	Multiple	Recovered in 12 months	
54178	Ether	Right middle	Yes	Yes	?	Yes	No	Single	Improved	
84947	Local	Right lower	Yes	Yes	?	Yes	No	Single	Recovered in 18 months	
96592	Local	Right lower	Yes	Yes	?	Yes	No	Single	Improved. End results unknown	Multiple abscesses, empyema right.
112995	Ether	Left lower	No	No	No	Yes	No	Single	Died 33 days after operation	
130276	Ether	Left lower	Partial	No	Yes	No	No	Single	Died 15 days after first stage operation	
157775	Ether	Left lower	Yes	Yes	?	Yes	No	.....	Died in 8 months, hemoptegia nephritis	
161775	Ether	Right middle	Yes	Yes	Yes	Yes	No	Multiple	Died 8 days after operation	
162774	Local	Right middle	Pneumothorax therapy						Recovery	Abscess, foreign body, bilateral bronchiectasis. Abscesses, lung, brain, kidney, spleen. Double pneumonia, early abscess.
169958	Ether	Right lower	Yes	Yes	Yes	Yes	No	Single	Died 12 days after operation	
169979	Ether	Left lower	No	Yes	Yes	Yes	No	Multiple	Recovery in 2 months	
173458	Ether	Right lower	Partial	Yes	Yes	Yes	No	Multiple	Died in 3 days, hemoptegia	
180755	Cocaine	Left upper	No	No	Yes	No	No	Single	Died in 2 days	
194204	Local	Right upper	Partial	Yes	Yes	Yes	No	Single	Improved	Abscess, right empyema, tuberculosis of right lung.
200833	Ether	Right lower	Partial	Yes	Yes	Yes	Slight	Single	Recovery. Plastic on fistula 1 year later	
202937	Ether	Right upper and lower	Partial	Yes	Yes	Yes	No	Single	Died 26 days after operation	
215058	Cocaine	Right upper	Yes	Yes	No	Yes	No	Single	Recovery in 3 months. Old tuberculosis	
216141	Cocaine	Right upper	Partial	No	Yes	Yes	No	Single	Recovery in 4 months	
236782	Cocaine	Right lower	No	No	No	Yes	No	Single	Recovery in 3 months	Vessel ruptured into abscess.
239753	Cocaine	Left upper	No	No	No	No	Yes	Single	Died in 7 weeks. Sudden hemorrhage	
242997	Cocaine	Right lower	Yes	No	No	Yes	Yes	Single	Recovery in 3 months	
246033	Cocaine	Right lower	No	No	No	No	No	Single	Died before drainage operation	
248236	Cocaine	Right upper	No	No	No	Yes	No	Single	Improved. Fistula 4 months	
248566	Cocaine	Left lower	No	No	Yes	No	No	Single	Improved. Op. pneumothorax	Abscess, bronchopneumonia, chronic nephritis.
228271	Cocaine	Right lower	No	No	No	Yes	No	Single	Recovery in 4 months	
240703	Cocaine	Right upper	Yes	Yes	No	Yes	No	Single	Recovery in 4 months	
250159	Cocaine	Right lower	Yes	Yes	No	Yes	No	Multiple	Died. Huge abscess, old empyema	
254476	Cocaine and ether	Right middle	Yes	Yes	No	Yes	No	Single	Recovery	

TABLE 12.—OPERATIVE FINDINGS IN SEVENTEEN CASES OF CHRONIC ABSCESS

No.	Anesthetic	Location of abscess	Pleural adhesions	Primary drainage	Pleural cavity opened	Pus found	Hemorrhage	Cavities	End results	Necropsy findings
36094	Ether	Right lower	No	No	No	No	Yes	.....	Not improved	Drained abscess
36479	Local	Right lower	Yes	Yes	Yes	Yes	No	.....	Died in 1 week	
41553	Local	Left lower	Yes	No	No	No	No	.....	Not known	
56674	Local	Right lower	No	No	No	No	No	.....	Not improved	Abscess, embolus, old emphysema, tuberculosis
57500	Ether	Left lower	Yes	Yes	.....	Yes	No	Single	Died 1 day after operation	None
74091	Ether	Left lower	Yes	Yes	No	Yes	No	Multiple	Died in 5 months	Abscess, empyema pericarditis pneumonia
10239	Ether	Right lower	Slight	No	No	Yes	No	Single	Improved	
114711	Ether	Right lower	Yes	Yes	No	Yes	No	Single	Improved (chronic bronchitis)	
116593	Ether	Right middle	No	No	.....	Yes	No	Multiple	Died 4 months after operation	
163709	Ether	Right lower	Yes	Yes	No	Yes	No	Single	Improved. Fistula	
193201	Ether	Right upper	Yes	Yes	Yes	Yes	No	Multiple	Improved. Fistula 7 months	Abscess, emphysema, bronchopneumonia
195209	Ether	Right upper	No	No	Yes	No	Slight	Single	Died 4 days after operation	Abscess, left empyema, emphysema
207626	Ether	Right middle	Yes	Yes	Yes	Yes	No	Single	Died 10 days after operation	
213924	Ether	Left lower	No	No	Yes	Yes	No	Multiple	Improved. Fistula 14 months	
235649	Cocaine	Left upper	Yes	Yes	No	Yes	No	Single	Recovery	
239564	Cocaine	Right lower	No	No	No	Yes	No	Multiple	Died 3 months after operation	Huge abscess
250153	Cocaine	Right middle	No	No	Yes	Yes	No	Multiple	Died 7 weeks after first operation	Multilocular abscess. Hemorrhage

TABLE 13.—OPERATIVE FINDINGS IN SEVEN CASES OF BRONCHIECTASIS

No.	Anesthetic	Location of lesion	Pleural adhesions	Primary drainage	Pleural cavity opened	Pus found	Hemorrhage	End results	Necropsy findings
48586	.....	Right lower	Yes	Yes	No	Yes	No	Improved?	Left bronchiectasis. Old tuberculosis right apex.
80279	.....	Right lower	No	No	Yes	Yes	No	Marked improvement. Fistula	
86333	Ether	Left lower	Yes	Yes	No	Yes	No	Suicide	
98902	Ether	Right lower	No	Yes	Yes	Yes	No	Still draining 3½ years after operation	Chronic saccular bronchiectasis. Left lung completely destroyed.
124560	Ether	Left lower	Yes	Yes	No	Yes	No	Died 1½ months after operation	
202460	Ether	Right lower	No	Yes	Yes	Yes	No	Improved; chronic sinus. Plastic operation	
218928	Cocaine and ether	Right lower	No	No	Yes	Yes	No	Improved; draining sinus	

for the first few days. In the presence of wide incisions drainage is comparatively simple. A rubber tube inside the gauze pack for the first few days followed by the use of rubber tissue drains has been found very satisfactory.

The findings at operation in the 54 operated cases herein reported may be seen in Tables 11, 12, and 13. Pleural adhesions were firm and extensive in only about 50 per cent of the cases. Such adhesions were present in only two of the 7 cases of bronchiectasis. Primary drainage operation was performed in five instances in which there were no firm adhesions. One of the patients died of empyema. In eleven instances in which the abscess was drained in one stage the pleural cavity was opened. Three of the patients died of empyema.

The abscess was located in the right lung in 74.5 per cent of the cases. The right lower lobe was involved in about 50 per cent. The cavities were multiple in 23.4 per cent of the cases.

In nine instances pus was not found at operation. Five of the patients died. Secondary operation was performed eight times. One patient operated on four times ultimately recovered. The important postoperative incidents are tabulated in Table 14.

TABLE 14.—POSTOPERATIVE INCIDENCE

	Cases	Fatal
Hemorrhage.....	7	2
Empyema.....	6	6
Secondary abscess.....	3	1
Hemiplegia.....	2	2
Massive gangrene.....	1	1
Pulmonary embolus.....	1	1
Extensive emphysema.....	1	1
Convulsions.....	1	
Temporary blindness.....	1	
Arthritis.....	1	

The results of operation may be seen in Table 15. Of the 54 patients operated on twenty died. Excluding one who died before the second stage drainage operation could be done, and one suicide, the mortality is 33.3 per cent.

In 1918, 17 patients presented themselves for treatment. All were operated on. The mortality, with the first exception just noted, was 23.5 per cent.

Two patients died of acute hemorrhage several weeks after operation. One died following a second drainage operation for metastatic pulmonary abscess. He had previously had a gastro-enterostomy for duodenal ulcer, drainage of a complicating empyema with bronchial fistula, and drainage of a large lung abscess following the empyema. One died of toxic gastro-enteritis complicating a chronic abscess (first drained elsewhere) involving practically a whole lung. It was impossible to get this patient into condition for thoracoplasty.

TABLE 15.—OPERATIVE RESULTS

1910-1919	Cases	Cured or improved	Not improved	Died
Acute abscess.....	30	20 (66.6%)		10 (33.3%)
Chronic abscess.....	17	7 (41.1%)	2 (11.7%)	8 (47%)
Bronchiectasis.....	7	5 (71.5%)		2 (28.5%)

TABLE 16.—POSTOPERATIVE SEQUELÆ

Secondary abscesses.....	4 cases
Bronchial fistulas, in cases of abscess:	
Spontaneous closure under 6 months.....	11 cases
Spontaneous closure after 6 months.....	2 cases
Plastic closure.....	1 case
Draining after 6 months.....	2 cases
Unknown.....	10 cases
Bronchial fistulas in cases of bronchiectasis	
Spontaneous.....	1 case
Draining one year or more.....	3 cases
Unknown.....	1 case

Postoperative sequelæ are enumerated in Table 16. It may be noted that bronchial fistulas occurred in 16 (34 per cent) of the abscess cases. Thirteen of the fistulas closed spontaneously. In the case of plastic closure done about one year ago, no complications have developed from the closure.

The necropsy findings in all fatal non-operative cases are indicated in Tables 17 and 18.

TABLE 17.—POSTOPERATIVE CASES OF ABSCESS NOT OPERATED FOR ABSCESS

Number	Diagnosis	Operation	Time of death after operation	Necropsy findings
73827	Hypernephroma	Nephrectomy	48 days	Abscess right lung, bronchopneumonia; chronic nephritis
98059	Subdiaphragmatic abscess	Drainage	57 days	Abscess spleen, liver perforative; abscess of right lung
101446	Tubo-ovarian abscess	Excision	46 days	Multiple abscess, pelvis, liver, lungs, subdiaphragmatic
125039	Duodenal ulcer	Gastro-enterostomy	33 days	Multiple abscess of both lungs; bronchopneumonia
128280	Cancer of rectum	Kraake	19 days	Multiple abscess both lowers; cancer of liver; left empyema
136560	Cancer of lip Drained for empyema	Block dissection	2½ months	Empyema (drained); abscess upper lobe each lung (tuberculosis both apices by x-ray; bronchiectasis)
139244	Exophthalmic goiter	Resection	13 days	Large abscess middle right
146356	Right pyonephrosis	Nephrectomy	19 days	Bilateral metastatic abscesses
166661	Cancer of uterus	Cautery	18 days	Multiple small lung abscesses
167134	Duodenal ulcer	Gastro-enterostomy	33 days	Right empyema (drained); small right lung abscess base upper lobe
168118	Cancer of stomach	Polya resection	40 days	Multiple small abscess of both lower lobes
187340	Cancer of esophagus	Witzel gastrostomy	9 months	Abscess both lower lobes; sinuses between esophagus and lungs
192433	Subdiaphragmatic abscess	Drainage	42 days	Subdiaphragmatic abscess, right empyema; large abscess right lung
208921	Cancer of sigmoid	First stage Mikulics	5 days	Multiple bilateral abscess; bronchopneumonia
232995	Cancer of stomach	Anterior Polya resection	22 days	Gangrene anterior upper lobes
235339	Double nephrolithiasis	Nephrolithiasis, pelviolithotomy	14 days	Multiple abscesses; perinephritic abscess
250653	Perforating gastric ulcer	Gastro-enterostomy	4 days	Multiple bilateral abscess

TABLE 18.—NON-OPERATED CASES; ABSCESS FOUND AT NECROPSY

Number	Diagnosis	Findings
74414	Chronic otitis media; cerebral abscess	Large cerebral abscess; abscess left lung
129069	Endocarditis pyemia	Multiple lung abscesses of both lungs; endocarditis; myocarditis
132370	Facial cellulitis	Multiple bilateral abscesses of both lungs
166081	Cardiac failure	Huge abscess of lower right. Bronchopneumonia
166605	Tuberculosis, anemia	Multiple abscess of both lungs, tuberculosis of right lower lobe
214322	Endometritis; peritonitis	Multiple embolic lung abscesses. Thrombosis vena cava
221055	Empyema	Drained empyema; multiple abscess of right middle and lower lobes

## SUMMARY

1. Pulmonary suppuration is of relatively more frequent occurrence than is generally recognized.

2. Suppuration occurs on a preceding inflammatory basis, or the infection is carried to the lung tissue through the bronchus, the blood stream, or by direct extension.

3. A persistent productive cough is the most characteristic symptom. The sputum is usually purulent and often foul. Other clinical features of suppuration are present in varying frequency and degree.

4. Localized dullness to percussion and a circumscribed x-ray shadow are the most constant physical findings.

5. Pulmonary suppuration is probably frequently mistaken for phthisis. In 33 per cent of the cases reported in this article symptoms were suggestive of tuberculosis.

6. Suppuration and a tuberculous infection may co-exist without anatomic or etiologic relationship.

7. The differential diagnosis of localized bronchiectasis and abscess may be impossible. Each predisposes to the other.

8. The treatment of localized suppuration is early free drainage. Prolonged expectant treatment or inefficient drainage greatly increases postoperative morbidity and mortality.

9. Local and regional anesthesia is safe and in most cases very satisfactory.

10. The abscess should be drained only through the adherent pleura or after the pleural cavity has been walled off by suture of the lung to the parietal pleura.

11. A two-stage operation allowing a few days for adhesions to form around the suture line probably is the best safeguard against empyema which is a frequent and the most dangerous complication.

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# FOREIGN BODIES OF DENTAL ORIGIN IN A BRONCHUS: PULMONARY COMPLICATIONS\*

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Foreign bodies of various kinds are undoubtedly lodged in the bronchi more frequently than they are recognized. Weist reported 1000 cases; 103 (10.3 per cent) only were from the literature, 897 (89.7 per cent) were unpublished cases collected by Weist by personal communications. It would seem possible that a correspondingly large proportion of cases of dental origin remains unpublished.

Foreign bodies of dental origin include teeth, dentures, instruments, and other material used in dental operations. Aspiration of infected blood or sputum is probably a more frequent source of infection than foreign bodies. The occurrence of such infection is obviously greatly more difficult to prove, but the frequency of gross mouth infection in patients subjected to dental operations needs hardly to be mentioned.

There have been at the Mayo Clinic during the past four years 7 cases of pulmonary suppuration following dental operations or trauma. In 2 cases the tooth was spontaneously expelled; in 1 it was discharged through a thoracotomy wound, and in 1 it was found at postmortem. In the other cases no foreign body was found, but it is quite probable that they were also cases of infection from inhalation.

I observed 6 of the 7 cases and have collected 45 proved cases from the literature. These 52 cases form the basis of this report.

## FOREIGN BODIES IN THE 52 CASES

Teeth.....	37
Artificial teeth.....	4
Dentures.....	2
Root canal broach.....	2
Dental burr.....	3
Allen's dental cement.....	1
Plaster of Paris.....	1
Hard rubber from gag.....	1
Blade of forceps.....	1

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\*\* Tabulated data concerning these cases may be found in the *Annals of Surgery* and in the reprints.

The foreign body was lodged in the right bronchus in 21 cases, in the left bronchus in 19, in both sides in 1, and in the trachea in 1; the location was not stated in 10. The bodies were most frequently in the right lower lobe.

In 26 cases the accident occurred during extraction under general anesthesia, in 12 under nitrous oxid, in 11 under ether, and in 3 under chloroform. In 3 cases false teeth were inspired; in 4 cases the foreign body was inspired during dental operations without anesthesia.

The literature contains more or less fragmentary reports of other similar cases (Carpenter, Ricketts, Stokes, McCrae).

*Symptoms and signs.*—The symptoms may be divided into those which are manifest immediately following the inhalation of the foreign body, and those which arise from its prolonged presence in the respiratory tract. The most constant and characteristic immediate symptom is cough of varying intensity and persistence; associated symptoms are dyspnea, cyanosis, wheezy respiration, pain in the chest, and nausea. In the 52 cases cough, more or less violent and spasmodic, was an immediate symptom in 27, pain or soreness in the chest in 13, and dyspnea in 10. In one instance cough started after twenty-four hours, in another after four days. In 12 there was no cough. In 4 cases dyspnea of a varying grade was the presenting symptom. In one only was there a sensation of a foreign body in a bronchus. It is noteworthy that in 7 cases (13.4 per cent) there were no symptoms whatever. In 16 of the series there were no serious pulmonary infections; in the remaining 36 there was evidence of pulmonary suppuration of varying grade. For convenience, in the further discussion the cases will be grouped on this basis.

In the 16 uncomplicated cases, the accident occurred during general anesthesia in 4, and during alcoholic intoxication in 1. No anesthesia was used in 2, and no statement was made as to anesthesia in 9. Symptoms were marked in 7, and not mentioned in 9. A diagnosis was made by the x-ray in 5; in one the plate showed only pleural thickening. In 8 there was no mention of an x-ray examination. With two exceptions the length of time the foreign body was present in the bronchus was short. In one a tooth was coughed up after three years; in another plaster of Paris fragments had been present for five years without symptoms other than a persistent spasmodic cough.

The foreign material was spontaneously expelled in 4 cases on the

third day, the fifth day, during the third month, and three years after accident, respectively. Early bronchoscopic removal was effected in 10. Two patients died, one from typhoid fever ten days after bronchoscopy, and one from tuberculosis following temporary recovery from an unsuccessful thoracotomy.

*Complications.*—This group comprised 36 cases. In 22 the accident occurred during the extraction of teeth under general anesthesia; in 2 others in which it followed extraction the anesthesia was not mentioned; in 2 loose artificial teeth or dentures were inhaled; in 1 a tooth was inhaled during a general anesthetic for an abdominal operation; in 1 pulmonary infection followed a kick in the face by a horse, resulting in the loss of several teeth.

*Immediate symptoms.*—In this group cough of varying severity associated with other symptoms, such as dyspnea, cyanosis, and pain in the chest, was manifest in 11. In 7 cases cough was the only symptom; in 3 there was no cough; in 10 there were no immediate symptoms, or they were so mild and transitory as to be practically negligible.

A latent symptomless period was present in 15. The length of the latent period was two weeks or under in 3, between two weeks and two months in 7, more than two months and under one year in 2, two years in 1, and eleven and one-half years in 1. There was no latent period in 13. The records in the remaining cases were indefinite on this point.

*Late symptoms.*—Cough, usually with purulent sputum, was present in 29 cases, hemoptysis in 8, and pain in the chest in 11. The onset of late symptoms was gradual and without any intervening symptomless period in at least 13. The relation was not stated in 8. X-ray reports were mentioned in 16. The plates showed the foreign body in only 4 cases, an artificial tooth with a piece of denture in 1, a tooth in 2, and a dental burr in 1. Abscess was shown in 5 cases; one case diagnosed tuberculosis proved on postmortem to be bronchiectasis. A fluoroscopic examination revealed limitation of movement of the diaphragm in one case; negative x-ray findings for foreign body were reported in 12 cases.

It would appear on first thought that a diagnosis should be established by the fact that a foreign body passed down the pharynx. In the present series of cases, the patient was usually unconscious at the time of the accident. In one case (Carpenter's) the patient believed that he had swallowed a denture with four teeth; its presence in the lung was never suspected and was only proved at postmortem

after thirteen years. In one case only (Hubbard's) did the patient insist that the foreign body was in the lung in spite of negative x-ray and other findings.

In cases without immediate severe symptoms the operator may believe or fervently hope that the foreign body passed down the esophagus instead of the trachea. In one case (Jarvis') the dentist obviously had such hopes, in spite of the fact that the patient, a physician, had paroxysmal cough and other characteristic symptoms of foreign body in a bronchus immediately on awakening from anesthesia. When the patient asked to see the tooth the dentist explained that it had broken and was thrown away. Three months later the physician coughed up the tooth.

In cases of multiple extraction, as in 22 instances in this series, a tooth or stump of a tooth is easily lost without being missed.

*Treatment.*—Bronchoscopy was done for the removal of foreign bodies in 5 cases, in 3 of which the x-ray showed the foreign body. In the fourth case a second x-ray plate, taken after a positive clinical diagnosis of foreign body had been made, showed the foreign body. In the fifth case no x-ray was taken. In 2 of these cases the foreign body was removed at the first attempt; in 1 two unsuccessful high bronchoscopies were followed by a third successful low bronchoscopy after tracheotomy; in a fourth the bronchoscopies failed. Dr. Jackson had seen this case and believed the foreign body to be beyond reach of the bronchoscope. In still another case in which bronchoscopy failed, a first-stage operation was done for drainage and the patient died before the second-stage operation had been undertaken. Thoracotomy was done in 15 cases, in 2 of these the lung was resected. In the remaining 13 cases the operation was done for drainage of the suppurating process.

*Results.*—Fourteen of the 36 patients with complications died; 16 made a complete recovery, and the result in the remaining 6 cases is not definitely stated. There were seven deaths in the 24 cases occurring since 1900.

Seven of the 14 patients who spontaneously expelled the foreign body recovered, and 3 died; the ultimate result was not stated or was uncertain in 4. In 3 cases an abscess requiring drainage developed after the foreign body had been expelled; in one case the foreign body was discharged through the drainage wound, and in one case the tooth was expelled after two and one-half years. Seven months

later an abscess developed, and after two months the patient died. In 15 cases in which thoracotomy was performed 2 were followed by resection of the lung; both patients died; one died of exhaustion, and one of pulmonary embolus before the second-stage drainage operation. One died while being chloroformed for drainage operation. One improved so markedly following the preliminary rib-resection that the second-stage operation was not done. In the remaining 11 cases, 1 patient died, 1 was greatly improved, and 9 made a complete recovery.

#### POSTMORTEM FINDINGS IN 9 FATAL CASES

1. Bilateral bronchiectasis, empyema, tooth in bronchus.
2. Pulmonary embolism.
3. Large empyema fistula in lung, denture in pleural cavity.
4. Abscess, ulcerated bronchus, tuberculosis.
5. Abscess, tooth in bronchus.
6. Abscess, empyema, tooth in bronchus.
7. Massive gangrene of entire lung, tooth obstructing bronchus.
8. Bilateral lower lobe bronchiectasis, tuberculosis, tooth in bronchus.
9. Bronchiectasis, pericarditis, tooth in bronchus.

#### DISCUSSION

In this series of cases the relationship between multiple extractions of teeth under general anesthesia and pulmonary complication is striking. Multiple extractions under general anesthesia were performed in 22 instances. Aspirative infection as a cause for pulmonary suppuration may probably be assumed to be sufficiently evident in the cases in which the tooth was later expelled, or in which an impacted tooth was found in the midst of a suppurative or gangrenous process in the lung. Perhaps the most striking evidence of all is shown in the case of Israël in which a tooth was found in an actinomycotic abscess of the lung. That aspiration of infected material from the mouth independent of teeth is a large factor in the causation of pulmonary infection cannot be so clearly demonstrated in the individual case, but much evidence has accumulated indicating that aspiration of infected material is one of the most common causes of abscess, gangrene, and bronchiectasis. As early as 1877, Schüller found that the introduction of clean foods into bronchi of rabbits through tracheal wounds is practically harmless, while the introduction of the same foods mixed with bacteria and filth result in a fatal pneumonia. Lung abscess following tonsillectomy has been reported frequently



(Manges, Tewksbury, Bassin, Frank, and others). Külbs found bad teeth and tartar (Zahnstein) in a large proportion of cases of lung abscess in which he operated. In a series of 56 cases of pulmonary suppuration at the Mayo Clinic in which operation was done, aspiration of an infection was probable in 25 per cent; the etiology was questionable in another 25 per cent, but it is probable that a large proportion of these were cases of aspirative infection.

The importance of early recognition of a foreign body in a bronchus is emphasized by the fact that in this series there was no mortality in the cases in which it was expelled or removed early by bronchoscopy. All the fatalities, with the exception of one death following lung resection, were in cases in which the foreign body had been present for a long period.

Positive diagnosis may be made by means of the history, the x-ray, or by bronchoscopy. It is important to remember, however, that each and all of these may be negative in the presence of a foreign body, as in 12 cases in this series. Symptoms and signs are suggestive, but in themselves are rarely conclusive. In many cases they have led to an erroneous diagnosis of tuberculosis.

The history of the case is of first importance. If the operator knows that a tooth has passed down the pharynx, and the patient immediately develops symptoms of bronchial irritation, the diagnosis is obvious. Even in the absence of symptoms, it should be assumed that the foreign body passed down the trachea rather than the esophagus until the contrary is proved. No marked immediate symptoms occurred in 9 of the 22 cases and there was a later symptomless period in 16 of 35 cases. In one case it was of thirteen years' duration. The profession has been slow to recognize that a symptomless period does not constitute proof of absence of a foreign body. Jackson writes on this point: "Practitioners are heedless of and even scoff at the patients suspicious that a long previously aspirated (or "swallowed")\* foreign body is the cause of present symptoms."

Examination by the x-ray is indispensable, and a positive plate establishes the diagnosis both as to the presence and the location of the foreign body. A negative x-ray, however, is not conclusive and in the presence of a diffuse shadow from pulmonary suppuration is of doubtful value. In the 16 uncomplicated cases in this series, the x-ray was positive in 6 of the 7 cases examined, but in the group with

\* Inserted by Hedblom.

complications it failed to show the foreign body in 12 of the 16 cases examined.

In early uncomplicated cases bronchoscopy in skillful hands is the best method both of diagnosis and of removal. The indications for bronchoscopy for a foreign body as enunciated by Jackson are as follows:

1. The appearance in the roentgenogram of a foreign body or of any suspicious shadow.

2. Cases in which a clear history is given of the patient's having choked on a foreign body, and in which the foreign body was not afterwards found.

3. Cases in which there are signs of stenosis of the trachea or the bronchus.

4. In any case suspected of bronchiectasis.

5. In the absence of any history of a foreign body, the patient giving symptoms of pulmonary tuberculosis, without the finding of bacilli in the sputum, and especially if the physical signs are at the right base, and above all, if there are also physical signs of pleural effusion.

6. In case of doubt, bronchoscopy should be done.

Jackson recognizes no absolute contra-indications to bronchoscopy.

### TREATMENT

Expectant treatment is employed in the hope that the foreign body may be expelled spontaneously; bronchoscopy and thoracotomy are the alternatives, after the foreign body has been recognized.

The question of the likelihood of the expulsion of the foreign body is often raised in the consideration of the advisability of bronchoscopy. In this series the tooth was expelled in only 3 of 13 cases before the onset of pulmonary suppuration. The tooth was expelled in 13 of 33 cases after suppuration had developed. Six of these patients recovered, but thoracotomy had to be done in 4 instances. Three patients who received no further treatment died. Jackson's attitude toward the question of spontaneous expulsion is as follows: "We do full justice to our patients when we tell them that while the foreign body may be coughed up, it is very dangerous to wait; and further that the difficulty of removal increases with each hour the body is allowed to remain."

If the foreign body has not been recognized, however, or the patient has been treated expectantly until suppuration has set in, the results following bronchoscopy are not so favorable. In 5 such cases in this series in which bronchoscopy was done the foreign body was removed in only one. It may be impossible to locate the tooth and it must be seen in order to be removed. Furthermore, its removal in the presence of pulmonary suppuration becomes only an incident. The important consideration in such cases is the suppurating focus. For this complication thoracotomy for drainage has given the best results. If the focus is in the form of a localized solitary abscess, a drainage operation is the operation of choice. If the cavity is multilocular or if there is a bronchiectasis, any form of treatment is likely to yield a high morbidity and mortality. Massive gangrene is uniformly and quickly fatal.

The table of postmortem findings is uncontrovertible evidence of the possible etiologic relationship of foreign body aspiration to abscess, gangrene, and bronchiectasis.

With regard to details of dental operative technic for prevention of accidental aspiration of foreign bodies, Dr. Gardner of the Mayo Clinic in a personal communication expressed himself as follows:

"The patient should be watched quite as carefully with a local anesthetic as with a general. The use of gauze sponges in no way interferes with the work of the operator; it prevents the inhalation of a foreign body during operation and cares also for the hemorrhage. Furthermore, the dentist may, by careful examination of the teeth before operation, ascertain if the prop might displace pieces of tartar, fillings, or even the teeth themselves during a general anesthetic. The condition of the patient undergoing any operation often requires the use of a gag during an ether anesthetic and the anesthetist should know the condition of the patient's teeth before the anesthetic is started, since such an instrument often displaces from a tooth foreign bodies which might be inhaled."

#### SUMMARY

1. Aspiration infection of the lungs is most common in operations about the mouth following general anesthesia.
2. Symptoms may be immediate and continuous or there may be an intervening symptomless period of months or years. There may be no immediate symptoms.

3. The most constant and characteristic immediate symptoms are cough, dyspnea, wheezy respiration, and pain in the chest. The late symptoms in varying number and degree are those of pulmonary suppuration.

4. Late symptoms of foreign-body infection often simulate phthisis, and that is the diagnosis often made.

5. Positive diagnosis rests essentially on history-taking, x-ray, and bronchoscopy. The history may be that of having "swallowed" the foreign body.

6. Bronchoscopy for diagnosis is indicated in any early doubtful case.

7. Spontaneous expulsion of small irregular foreign bodies, of high specific gravity, especially teeth, is always doubtful. Spontaneous expulsion often occurs only after an abscess has formed.

8. Bronchoscopy is the only treatment to be considered in early uncomplicated cases. In cases in which there is suppuration, thoracotomy for drainage gives the best results.

9. In fatal cases death is usually due to abscess, bronchiectasis, or gangrene of the lung, any of which may be complicated by empyema.

10. Tuberculosis may coexist with a suppurative process.

#### CASE REPORTS

Case 1 (169958).—E. R. F., aged 34, an anemic, emaciated woman came to the clinic Aug. 21, 1916, complaining of cough with sputum, pain in the back, fever, weakness, and loss of weight.

The illness began in January, 1915, following teeth extraction under general anesthesia. The patient began to cough immediately on awakening from the anesthesia and the cough persisted. Pulmonary tuberculosis was diagnosed for which she was treated for a number of months. September, 1915, an x-ray was taken and a tooth was revealed in the lower part of the right lung. Three attempts were made to remove the tooth by bronchoscopy but all failed. Thoracotomy was then done but the tooth was not found.

When the patient came to the clinic her cough was very severe and persistent, preventing sleep. Pain in the back with fever had started six weeks before. She had lost 30 pounds in weight. The sputum was fetid, greenish and amounted to upward of a pint in twenty-four hours.

At the time of examination the hemoglobin was 76 per cent, the leukocyte count 17,600, the systolic blood pressure 117, the diastolic 60, the pulse 96, and the temperature 100.5°. Resonance was impaired and breath sounds were diminished at both bases. There was a scar of thoracotomy below the angle of the right scapula. The skiagram showed shadows at both bases which were believed to be



FIG. 386 (169958).—Roentgenogram made eight months after teeth extraction.

due to the thickened pleura at the right and a small amount of fluid at the left base. The appearance of the right lower lobe suggested tuberculosis. The clinical diagnosis was old abscess of the right lung, and left pleurisy with effusion. August 25, a bronchoscopic examination was made. The tooth was not found but much pus was seen coming from the right bronchus. Thoracentesis of the left pleural cavity yielded pus. August 28, a first-stage operation was done for drainage of the abscess. The patient died, however, before the second-stage drainage operation could be performed.

Necropsy showed a bilateral bronchiectasis and left empyema.

The broken tooth, surrounded by an abscess, was found lying within 2.5 cm. of the lower surface near the lateral aspect of the lung (Figs. 386 and 387).



FIG. 387 (169958).—Bronchiectatic lung showing tooth impacted in dilated terminal bronchus of right lower lobe. Tooth aspirated into bronchus during multiple teeth extraction under general anesthesia. Diagnosis of foreign body in bronchus made only after nine months.

**Case 2 (216141).—**J. R., a man aged 66, came for examination Dec. 8, 1917. This patient appeared older than his years, probably due, in part, to exposure and to alcoholic excess. His illness began in October, 1917, after teeth extraction under ether anesthesia. A number of

teeth were broken off, and considerable bleeding followed for two weeks. Immediately after the operation the patient developed a constant dull pain in the right lower chest anteriorly. These symptoms persisted for two weeks, when he suddenly vomited a pint of pus; coughing and a large amount of purulent sputum persisted, especially during the month before examination, and kept him awake a great deal at night.

Examination of the chest showed an area of flatness in the right axilla. The hemoglobin was 50 per cent and leukocyte count 13,000. The systolic blood pressure was 140, the diastolic 66, the pulse 84, and the temperature normal. Repeated sputum examinations were negative for tuberculosis bacilli. The skiagram showed dense infiltration in the upper portion of the right lobe with cavitation. The patient was a poor surgical risk and he was kept under observation in the hope that there might be some improvement. His symptoms instead of subsiding, however, became more aggravated. Four weeks later the skiagram showed marked extension of the purulent process; operation was therefore advised. The patient was transfused once before the operation by the sodium citrate method, receiving one-half liter of blood. A two-stage drainage operation under local anesthesia was performed because of the absence of pleural adhesions. An abscess cavity of about 400 c.c. capacity containing a mass of gangrenous lung tissue was found. The patient's convalescence was rapid; four months after the operation he had gained 50 pounds in weight. He was dismissed from the clinic with a small sinus. Five months later a portion of a tooth was found in the dressings. The sinus then rapidly closed. In September, 1919, the wound was solid and there were no symptoms referable to the old pulmonary lesions.

Case 3 (235649).—Mrs. N. F., aged 39, presented herself at the Mayo Clinic June 18, 1918, complaining of persistent cough with purulent sputum and occasional hemoptysis. Her illness began in August, 1917, following teeth extraction under ether. The day following the operation she coughed up 4 or 5 ounces of dark, clotted blood having a very foul odor. She continued to cough and to raise large amounts of pus and blood. She also developed pleurisy with effusion for which a thoracotomy was performed in September, 1917, and a secondary operation for drainage in November.

The patient coughed frequently during the examination, raising a bloody purulent sputum having a very foul odor. There was dull-

ness in the left axilla, moist râles, and tubular breathing toward the apex. The hemoglobin was 80 per cent and the leukocyte count was 9,400. The systolic blood pressure was 126, the diastolic 70, the pulse and temperature normal. There was distinct clubbing of the fingers. The sputum was repeatedly examined for tuberculosis bacilli but none were found. The skiagram showed infiltration of the

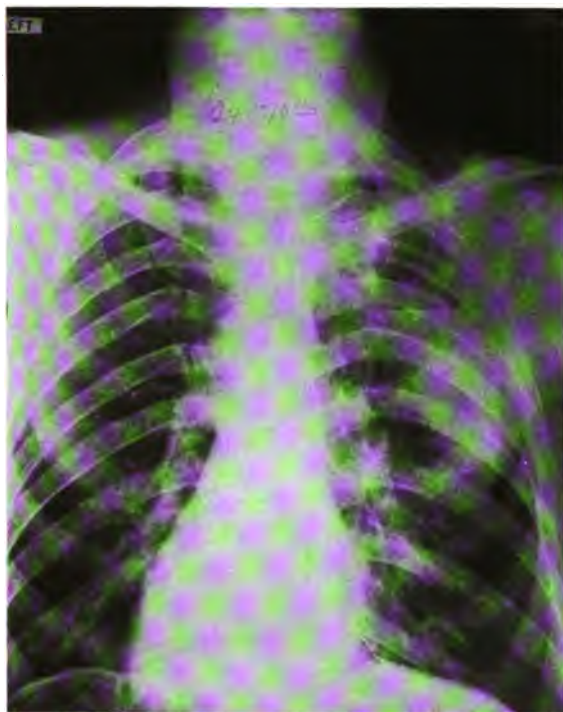


FIG. 388 (240703).—Roentgenogram made before operation about two and one-half months after teeth extraction. Note the fluid level.

lower left lobe of the lung, and a diagnosis of probable abscess was made. An exploratory aspiration was performed in the region of the thoracotomy incision. The first operation was interrupted by an epileptiform seizure followed by lapse of consciousness for about five minutes. Six days later a tubular cavity was opened and drained. The patient left the hospital two weeks later; the wound drained for some weeks and then closed. There have been no further symptoms.

Case 4 (240703).—J. K. S., a man aged 45, came for examination Aug. 1, 1918. He appeared to be very sick and complained of cough

'19—64



with much foul sputum. He had had several teeth extracted in May, 1918. Two weeks later he began to cough, raising foul-smelling sputum, sometimes 24 ounces each day. Slight swelling of the legs had been noted.

The physical examination disclosed marked loss of weight, foul breath, systolic blood pressure 110, diastolic 60, pulse 80, and temperature 98. The right chest wall was markedly retracted and there was



FIG. 389 (240703).—Roentgenogram made eighteen days after operation.

an area of dullness about the level of the second and third ribs anteriorly. Breath sounds in this region were intensified. No tuberculosis bacilli were found in the sputum. The skiagram showed marked infiltration in the upper right lobe which was diagnosed abscess with cavitation. The fluoroscopic examination revealed a fluid level with distinct splashing.

A two-stage operation was performed for drainage of the abscess, which was found to lie about in the midaxillary line. The abscess contained little pus, but some very foul smelling necrotic tissue was

removed. The convalescence was slow although progressive, and the patient left the hospital with a bronchial fistula. Jan. 19, 1919 the patient reported by letter that he had gained 38 pounds in weight, that the fistula had closed, and that there were no symptoms referable to his former illness (Figs. 388 and 389).

**Case 5 (281586).**—J. A. C., a rather frail looking man, aged 63, came to the clinic July 23, 1919, complaining of cough with sputum,



FIG. 390 (281586).—Roentgenogram made nine days before operation.

weakness, and loss of weight. His illness began in October, 1918, when he was kicked in the face by a horse. The kick was a glancing blow, breaking the bridge of the nose and knocking out several teeth. He was knocked unconscious by the blow. There was some cough immediately on recovering consciousness, and the patient believes that he must have swallowed a great deal of blood because his stools were black following the accident. Eight weeks later a corrective operation under cocain was done on his nose. He then had a mild attack of pneumonia; he was in the hospital for four weeks,

and had several attacks of hemoptysis. One month after recovering from the pneumonia he developed severe pain in the right chest with fever running up to 103°. Twenty-four hours after the onset of this illness the "abscess broke," and a pint of pus was coughed up. There had since been a persistent cough with sputum, amounting to about 500 c.c. in twenty-four hours, progressive weakness, and a weight loss of between 20 and 30 pounds (Fig. 390).

Slight dullness was found at the right apex anteriorly, with marked amphoric breathing. The respiratory excursion at the right apex was lagging. Many teeth were missing, and those remaining showed marked pyorrhea and some were carious. The hemoglobin was 58 per cent, and the leukocyte count 16,000. The systolic blood pressure was 134, the diastolic 84, the pulse 88, and the temperature 101°. Sputum examination for tuberculosis bacilli and elastic tissue was negative. The skiagram showed a large abscess in the upper lobe of the right lung. The clinical diagnosis was probable aspiration abscess. A two-stage drainage operation was performed as pleural adhesions could not be definitely made out. A deeply situated abscess about 3 inches in diameter was opened and drained. The convalescence was uneventful and the patient went home three and one-half weeks following operation in good general condition. He had no cough or sputum at this time and had gained 15 pounds in weight.

Case 6 (274952).—Mrs. J. S., a thin, rather frail looking woman, aged 30, presented herself June 12, 1919, complaining of headache and pain in the abdomen which began following childbirth January, 1919. In May, 1919, the patient was given ether for teeth extraction. She began to cough immediately on awakening from the anesthesia. The cough, paroxysmal in character and worse at night, continued and was accompanied by more or less pain in the lower substernal region. The expectoration was mostly foamy mucus and moderate in amount. Perspiration was profuse at night; vomiting was frequent.

The patient was a poorly developed woman with marked evidence of loss of weight. At the time of examination the hemoglobin was 64 per cent, and the leukocyte count 9,000. All the teeth were missing. There were râles and increased breath sounds at the right apex. The right base was dull to percussion. The sputum was negative for tuberculosis bacilli. The x-ray examination showed pleural thickening with probable fluid at the right base. The diagnosis was that of general debility with probable slight right pleural effusion. The ques-

tion of the presence of a foreign body was raised, but there was no definite evidence, and the patient was discharged without surgical treatment. June 15, 1919, during a very severe paroxysm of coughing she expelled a tooth. The cough and expectoration immediately became somewhat less, but at the last report, Aug. 7, 1919, she still had pain in her back and some cough (Fig. 391).



FIG. 391 (274952).—Roentgenogram made two days before expulsion of tooth.

**Case 7 (286912).**—Mrs. A. K., aged 33, presented herself Sept. 1, 1919, complaining of a cough with purulent sputum, weakness, and loss of weight. The onset of her illness dated back nineteen months, following extraction of many teeth under general anesthesia. She began to cough immediately on awakening from the anesthesia; the cough persisted. Six weeks after the teeth extraction she coughed up two pieces of tooth, and twelve weeks later a silver filling. The cough, however, continued, the sputum was foul and amounted to about 500 c.c. in twenty-four hours. She had pain in the right chest, night sweats, and occasional hemoptysis. The symptoms instead of sub-

siding after the foreign body was expelled became progressively worse.

At the time of examination the patient was sitting with a basin before her, coughing more or less continuously, and raising very foul purulent sputum. The systolic blood pressure was 100, the diastolic 60, the pulse 72, the hemoglobin 80 per cent, and the leukocyte count 5,000. The sputum examination was negative for tuberculosis



FIG. 392 (286912).—Roentgenogram made about one and one-half years after patient expelled two fragments of teeth and silver filling.

bacilli. The skiagram showed a questionable shadow just behind the heart at the cardiophrenic angle. Because of the incessant cough and large amount of sputum, it seemed advisable to do an exploratory operation notwithstanding the meager x-ray and physical findings. Sept. 6, 1919, a first-stage operation was done for drainage of the abscess. Portions of the ninth, tenth, and eleventh ribs were resected, and the lung was sutured to the parietal pleura. Pneumothorax had not occurred so far as it could be ascertained. A week later an explora-

tory aspiration was performed for abscess. The aspiration yielded only air which was entirely without odor. Following this negative aspiration the patient began to improve, the cough and sputum practically ceased within a week, and the patient began to gain in weight. It seemed probable that a local pneumothorax had been produced which was sufficient to bring about the good results. A letter from the patient's family physician October 17 stated that she was in excellent condition, but October 30 a second letter was received stating that there was a recurrence of the cough and sputum (Fig. 392).

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## UNUNITED FRACTURES OF THE HIP\*

M. S. HENDERSON

Fractures of the neck of the femur, commonly called fractures of the hip, occurring as they often do in the elderly person, present surgical conditions demanding the greatest care both in diagnosis and treatment. While this is true of all recent fractures of the hip, it is doubly true with regard to the treatment in the unfortunate group of cases in which bony union has failed. It is to the patients in this latter group that our attention is directed in this paper. A review was made of 120 cases of fractures of the surgical neck of the femur in which bony union had failed. While in a few instances fibrous union had become sufficiently firm so that restricted activity was possible without the aid of crutch or cane, in not a single instance, to our knowledge, except following operation, had bony union occurred.

It was our endeavor to determine if possible the reason for the non-union, whether operative procedures are justifiable, and, if so what type of case is the most suitable for surgery. Ordinary manipulative procedures, such as Whitman's abduction method or Cotton's impaction method as applied to recent fractures, were not considered. By the term surgical procedure is meant the opening of the joint and the exposure of fragments, with such measures as seem best to promote union. It has been suggested by Brackett to place the tip of the trochanter, denuded, against the denuded head and thus attain bony union, but with this I have had no experience.

There were 68 males and 52 females in the series. Twenty-six patients were operated on, and 94 were dismissed, nothing having been attempted to relieve the condition. Five patients were between 20 and 30; 20 between 30 and 40; 20 between 40 and 50; 46 between 50 and 60; 24 between 60 and 70; 4 between 70 and 80, and one between 80 and 90.

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After carefully reviewing the case records of these patients, the outstanding points established were that the non-union in the majority resulted from an incorrect diagnosis at the time of the accident, and that in the minority, even when the proper diagnosis had been made, no treatment had been carried out, often, it is true, for some justifiable reason. In a certain few the measures used had been rather in the form of a surgical ritual and were not in any sense of the word adequate. It was astonishing to ascertain how often elderly persons, who after a severe fall were disabled on account of intense pain in the hip, were told without being carefully examined that they were suffering from a sprain, the fracture not being diagnosed until months later, usually by another consultant. Another somewhat common story was that the physician who was called in, carefully measured the legs and finding no shortening or eliciting no crepitus, diagnosed a sprain without resorting to roentgenography. Weeks or months later, a consultation necessitated by continued disability revealed shortening of the affected leg, crepitus on manipulation, and a roentgenogram established the diagnosis of fracture. The probable explanation of this is that what was originally a more or less weakly impacted fracture, broke down through inadequate fixation of the limb. In none of the cases in this series was there a history of really proper treatment for the fracture. Good treatment had been instituted in a few instances but for some reason it was not prolonged enough. The patient may have been unruly, the supervision too weak or, complications, such as impending pneumonia, may have necessitated a discontinuance of treatment.

The fact that of the entire series of 120 patients, 94 were, for various reasons, denied the benefits of surgery, clearly shows that ununited fractures of the hip are not popular surgical risks. The mortality rate in the group of 26 patients was nil and in none of the cases did symptoms that were regarded as serious develop after operation. It is very evident that we must look farther to explain the low operative percentage. From a technical point of view, the operation is formidable. The incision must be large enough to permit of as free an approach to the hip joint as possible and care is required to prevent contamination during the manipulations necessary for exposure of the fragments. If an autogenous bone graft is to be used, the procedure is further complicated by a second wound and its care. Many of the patients are old, and have a low expectancy. The length of time necessary to complete the treatment and convalescence is

comparatively great, and the general health in the elderly is often such that it does not seem justifiable to subject them to the risk of the operation and the confinement. The reparative properties of bone in persons of more than 45 or 50 years is not so great as in younger persons. The social status of the patients may be such that they cannot afford to pay even their living expenses while under care. Many patients present themselves years after the accident when the neck of the femur is completely absorbed. In cases otherwise suitable for operation total absorption of the neck of the femur occurs, and it has been learned from this study that so far as any of the procedures herein considered are concerned, operation should not be done. The fact that in our experience bony union is difficult to secure by any means at present known, considered with the aforesaid difficulties, is sufficient to make us very cautious with regard to prognosis. In some instances, all things considered, surgery is advisable, but knowing that the results are uncertain one does not feel justified in strongly urging the patient to submit to the operation.

It is unfair to take the percentage of cures that resulted in the 26 patients operated on as a standard. We now know that not a few of this group who were subjected to operation were not the best subjects for surgery. Conclusions will, therefore, be drawn rather from the clinical experience gained than from any of the tabulated statistics. Twenty males and 6 females were operated on. Two were between 20 and 30; 6 between 30 and 40; 7 between 40 and 50, and 11 between 50 and 60. The duration of the non-union varied from three months to three years, an average of thirteen months. Nails or screws were used in 8 cases, and bone in 18. There were, as I have stated, no deaths, and infection, which fortunately was not serious, developed in but 2. The operative field is rather difficult to keep clean in these cases, but a fracture table, such as the Hawley table, makes the entire procedure easier. Plenty of assistance must be available, and the best of technic and care must be taken to provide proper postoperative fixation. It has been our experience that a plaster of Paris cast affords the best means of maintaining the proper position. There is some controversy whether the bone graft or the metal pegs should be used. Both are foreign bodies but the bone graft is absorbed. Consecutive roentgenograms of given cases show that the bone graft is gradually absorbed and is replaced by bone normal to the neck of the femur. Some of our patients treated with metal nails and screws

have them in place years later with no inconvenience. We have used nails and screws, autogenous bone grafts, and beef-bone screws. The last named are not best suited for the type of case under discussion but are most convenient in operating on recent fractures of the hip.

Eight patients were operated on with metal as a fixative, 3 with beef-bone screws, and 15 with autogenous bone grafts. Various methods were employed with the bone graft. First the peg obtained from the tibia was tried; later packing the space between the head and the neck with bone was tried by placing therein two or three short grafts. It was hoped thus to reestablish a portion of the neck, but both of these methods have been abandoned for the use of the fibula as advised by Davison. The curved U shaped incision, is used. The tip of the trochanter is removed, the method popularized by Murphy, as this has been found to give the best approach to the joint, and at the same time to give opportunity for inspection. In placing the graft from the fibula, care must be taken that the tunnel through the trochanter and the hole in the head are made the proper size so that the fit is snug but not too tight, and that the angle at which the graft is placed is at least the normal angle of the neck to the shaft of the femur. Fixation in a plaster of Paris spica cast, extending from the foot to the chest with the hip held in abduction, is maintained for at least three months. A great deal of comfort will be afforded the patient if the cast is not extended up on the chest wall on the side of the affected limb; this is not necessary for fixation since the limb is already in abduction.

It is not so easy as might be supposed properly to place a bone peg in a fractured hip. Care must be taken that the channel for it in the trochanter is correct. The peg must be placed deep enough in the head, which is often poorly nourished, to get a good hold, but not so deep that it engages the acetabulum for in such cases a fixed point is formed on the pelvis and any appreciable motion of the thigh will act as a fulcrum and throw so much strain on the graft that it will break (Fig. 393). If the peg is properly placed, the head travels quite easily with the graft which readily stands the strain until sufficient new bone has formed to make bony union complete (Fig. 394).

The end results of the operation in 7 of the 26 patients are not known; 10 operations were successful; 8 are known to be failures, and 1 patient is still under observation, but the result promises to be good. Thus there are 38 per cent good results, namely, bony union and good



**FIG. 393.**—Fracture of bone peg (tibia) probably due to fact that the bone peg was driven in so far that it engaged the acetabulum.



**FIG. 394.**—Bone peg (fibula) properly placed.

function. Of the entire series of 120 patients coming for relief, only 10 (8.3 per cent) were improved.

#### CONCLUSIONS

1. The most common cause of non-union is that the fracture is not recognized at the time of the accident. The disastrous result, therefore, is the result of no treatment. In cases in which the diagnosis is correctly made the treatment is often faulty and weak. An impacted fracture must be kept impacted until united.



FIG. 395.—Total absorption of the neck of the femur in a female aged 25, six months after accident.

2. As a group taken at large, ununited fractures of the hip offer a comparatively small percentage suitable for surgery; 26 (21.6 per cent) of the 120 patients were operated on. In 10 of the patients operated on (38 per cent) the operations were successful, giving, however, for the entire group of 120 only 8.3 per cent successfully treated.

3. Advanced age, poor general health, and so forth are contra-indication to operation, but the chief contra-indication is absorption of the femoral neck. A person of 25 may, in five months after the accident, show so much absorption of the neck of the femur (Fig. 395) that none of the measures herein considered offers any hope.

4. Any means, in suitable cases, that will freshen the fractured surfaces and maintain them in apposition is sufficient, but autogenous bone pegs are the most ideal.

5. From our experience, the fibula seems to be the best piece of bone to be used; it is easily obtained, and is never missed by the patient if it is removed anywhere 4 inches above the external malleolus.

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## THE SURGICAL TREATMENT OF BUNIONS\*

C. H. MAYO

The value of good feet is not appreciated until middle age when they are compelled to carry a greater weight than during youth and when new shoes must be fitted to the feet rather than the feet to the shoes, as in the second and third decades of life when the feet have often

become molded to abnormal types of shoes. Shoes are often too short or misshapen at the toe, causing the joint of the great toe to turn outward, and thus developing a hallus valgus. The deformity is in females in the majority of cases; a heel  $2\frac{1}{2}$  inches high makes it necessary to walk on an inclined plane. This enlarges the sesamoids and at times even develops them under the fifth metatarsal head.



FIG. 396.—Hallus valgus.

Hallus valgus is a very common deformity in which the great toe overlaps or compresses the second and third toes (Fig. 396). It is often associated with some degree of bunion. Bunion, except of the bursal type, rarely occurs without hallus valgus. The overgrowth of bone (Fig. 397) on the inner side of the first metatarsal bone is immediately back of the articulation. This has been

generally attributed to intermittent pressure; nevertheless an x-ray picture of the foot with severe hallus valgus and deformity from bunion shows a wide space between the heads of the first two metatarsals (Fig. 398). If the growth of bone were due to an intermittent pressure bony

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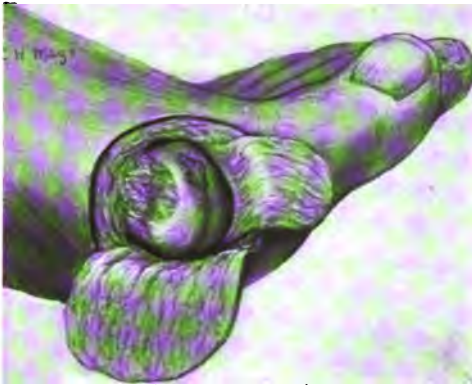


FIG. 397.—Bony deformity in bunion.



FIG. 398.—X-ray of foot with bunion showing exaggerated space between inner and outer metatarsal bones and displaced sesamoid wedges.



deformities would occur in other regions subjected to intermittent pressure, for example on the shoulder of the hod carrier or beneath the collar of the work horse. Is this overgrowth a protection incident to the deformity, hallus valgus, and an effort on the part of nature to protect the exposed or lightly covered inner side of the articulating head? It is more probable that this overgrowth at the terminal whirls of the capillary circulation where the joint capsule is attached to the periosteum is of the same origin as the overgrowth which occurs in rheumatoid arthritis, a mild chronic infection, the localizing factor



FIG. 399.—X-ray of foot with bunion showing lateral view of sesamoid.

being that of traumatism, since such growths occur and increase during the period of life in which rheumatism and recurring infections occur. The various shapes of feet and the limited number of shapes of shoes are undoubtedly responsible for the development of bunions and hallus valgus, conditions which occur more commonly in feet in which the great toe is longer than the second and third supporting toes, since the leverage action of the misshapen pointed and too short shoe turns the toe outward. Bunion rarely occurs on a foot whose great toe is shorter than the second and third toes, namely the square foot.

Flat-foot is a common deformity, either congenital or acquired. Persons of the colored race naturally have a low arch; the outline of the imprint of a wet foot indicates that the majority of them are flat-footed. The claim is possibly correct that the negro has more of the fatty pad on the sole of the foot beneath the instep than the white man, and that the flat foot in this naturally bare-footed race is more apparent than real and serves somewhat the purpose of the frog in the horse's foot. In later life flat-foot may develop from the

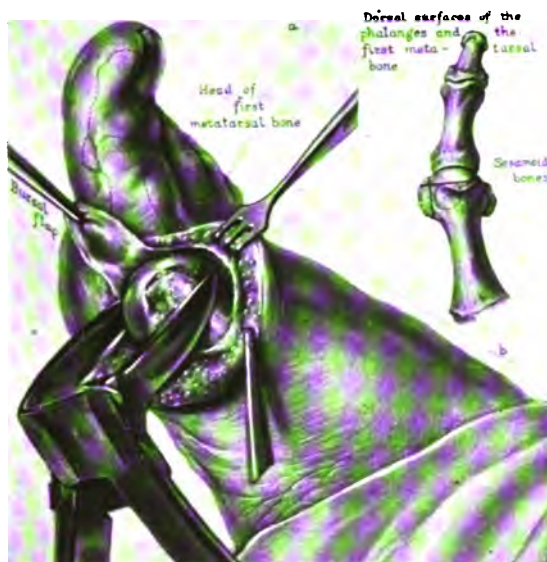


FIG. 400.—(a) Removal of head of metatarsus. (b) Angle at which head of metatarsus is removed, showing short incision at right angle to long incision.

breaking of the arch, or slow giving way of the arch, a condition which is associated with arthritis more commonly than is supposed, and which belongs to the period in which bunions develop. The complication of flat-foot with bunion is serious as recovery from operation is slower and the degree of benefit is much less than in cases without this complication.

Beneath the head of the great toe are the triangular sesamoid bones on either side of the flexor tendon. They are half an inch long and one quarter inch wide. I believe Robinson is correct in his assumption that on displacement of the flexor tendon in hallus valgus the sesamoid bones slip to the inner side of the head of the great toe and become a

bony wedge at each step, forcing apart the first and second metatarsal heads. This change of position is definitely shown when the body weight is added at the time the x-ray is taken (Fig. 399).

There are several methods, according to the condition, of the treatment of bunion:

1. Simple excision of the bunion bursa. Few operations are done in this early stage.
2. Excision of the bursa with removal of the inner side of the head of the first metatarsal.
3. The removal of all, or nearly all of the head of the first metatarsal. This procedure is too radical.



FIG. 401.—Suture to hold bursa in joint and straighten the toe.

4. The Keller operation in which the bony growth with the bursa is removed. Tendon relaxation is secured by removal of the concave articulating surface of the first phalanx.

5. The Robinson operation for removal of the sesamoid bones, the bunion bursa, and by means of bone forceps, the removal of the overgrowth of bone.

6. The usual operation performed for the relief of bunion is one I advocated many years ago for shortening the great toe and relaxing the extensor tendon; one quarter inch of the articulating surface of the head of the metatarsal bone is removed (Fig. 400) and motion is maintained by turning the bunion bursa into the joint in front of the divided bone surface after the removal of the bony overgrowth (Fig. 401). This was one of the first arthroplastic operations devised for articulating joints to maintain motion after severe surgical traumatism. The operation has been most successful except in cases of

marked flat-foot in which the pain of bunion is increased by a fallen arch complicated by mild arthritis. In such cases of flat-foot, hallus valgus, and bunion, I believe the head of the bone and the bunion bursa should be preserved; the overgrowth of bone and the sesamoid bones should be removed (Fig. 402). If the hallus valgus is marked the tendon of the extensor hallucis longus is split for one half inch over the joint and sectioned at the top on the inner side and at the bottom on the outer side; the divided split tendon is allowed to slip one quarter inch and is resutured.

Persons with hallus valgus and normal or possibly lowered arches are operated on by making a curved incision convexly upward over the inner side of the joint. The skin is deflected downward, the bunion

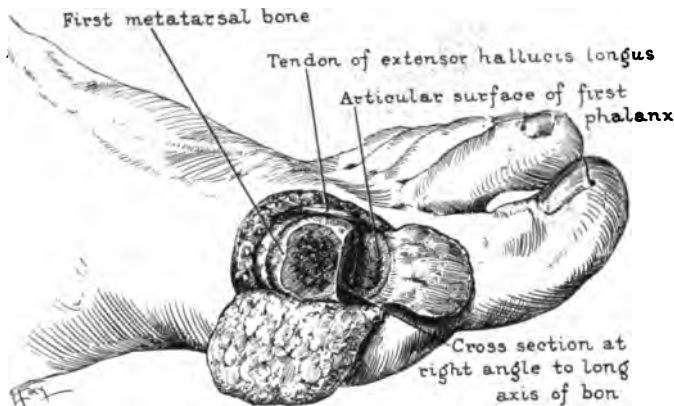


FIG. 402.—Excision of bony overgrowth and part of the head of the bone with preservation of the bursa.

bursa is dissected forward and the joint opened, the bursa being left attached to the inner surface of the first phalanx. One quarter inch of the head of the articulating surface is removed by bone saw or large bone-biting forceps. This relaxes both extensor and flexor tendons. The bony projection on the inner side of the head of the great toe is removed and the bunion bursa turned into the joint and held by sutures of catgut which also serve to straighten the great toe, thus removing the valgus. The wound is closed without drainage (Fig. 403). If the bunion is complicated by a marked flat-foot and hallus valgus I believe that the Robinson operation of removal of the sesamoids is indicated; the incision is the same, and the bunion bursa with the bony overgrowth is removed. If the great toe is bent downward the

white flexor tendon with the yellower surface of the sesamoids may be seen on each side of it. These bones can be removed with a knife or sharp pointed scissors if they are grasped with strong tenaculum forceps. In some cases of marked hallus valgus the extensor tendon should be lengthened.

It should be explained to patients who have flat-foot complicated with bunion that they have an added trouble which will delay the relief ultimately to be obtained. The sesamoid and the articulating surface should not be removed from the same foot, and for the majority



FIG. 403.—Closure of the wound.

of patients the operation I described first is more satisfactory. Early use of the foot following these operations is indicated. The patients should be up early, and at the end of the first week using the heel and outer side of the foot. As soon as possible, often within fourteen to twenty-one days, a stiff-soled shoe may be worn.

The operation is safe, easy of accomplishment, and the results are good. The operation should be advised more frequently. Advice should also be given with regard to the size and shape of shoes to be worn following the operation.

It is to be hoped that the many surgeons interested in orthopedics

as developed by the war will use their influence both on the manufacturers and the wearers of shoes to secure an improvement in the shape and length of shoes and thus aid in the prevention of many foot troubles which are wholly due to faulty fitting during early life.

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# BENIGN XANTHIC EXTRAPERIOSTEAL TUMOR OF THE EXTREMITIES CONTAINING FOREIGN-BODY GIANT CELLS\*

A. C. BRODERS

The word "xanthic" is defined as "pertaining to or tending toward a yellow color." The yellowish tint is the most striking feature of the benign extraperiosteal tumor of the extremities which contains foreign-body giant cells. This tumor has masqueraded under various names such as spindle-cell sarcoma, myeloid sarcoma, myeloid tumor, myeloma, myeloid endothelioma, myeloxanthoma, granuloma, giant-cell tumor, and giant-cell sarcoma.

Heurtaux, in 1891, differentiated true sarcomas and "giant-cell tumors that are marked by different characters and do not have any tendency to invade the neighboring tissues or organs," which he terms myelomas.

Targett, in 1897, considered the "giant celled tumors of the integuments" to be, clinically, as well as histologically, malignant growths. The presence of the polynuclear giant cells in the four tumors which he examined suggested to him "that the growths had originated from some bone-forming membrane, such as the periosteum and endostium but they were all in the integuments, superficial to the muscles and the tendons, and growing toward the skin rather than in the direction of the bones."

Dor, in 1898, writes that this type of tumor "deserves the name myeloxanthoma." His theory is that "the xanthomatous cells and the giant cells are the result of totally different processes of evolution, but they are derived from identical cells; in the first case the cells remain isolated; in the second case they fuse and their nuclei blend, making a single cell with multiple nuclei."

Bellamy, in 1901, stated that "though a myeloid tumor in the sense that it contains an abundance of giant cells among its tissue elements,

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the growth possesses no true claim to be regarded as a member of this class. . . . The fact that the evolution of the tumor is due to the proliferation of the endothelial cells of the blood vessels stamps it as an endothelioma; in view, however, of the large part taken by giant cells in its composition, it seems rather to merit the name of "myeloid endothelioma."

Fleissing, in 1913, first distinguished the extraperiosteal growths of the tendon sheaths from neoplastic growths. He states that the tumors called myelomas or giant-cell sarcomas which appear in the tendon sheaths of the fingers, the toes, the hands, the feet, and most probably, the forearm and the leg below the knee, are in reality not true tumors. They are not giant-cell sarcomas but inflammatory granulation growths. Their simplest designation would be granuloma of the tendon sheath.

Tourneux, in 1913, collected in his very extensive review of the literature on sarcoma of the tendon sheath 93 cases; about 54 of these should be classed as xanthic tumors with foreign body giant cells. A few of the interesting points of this series are as follows: There were 28 males and 26 females; the average of the ages given for 51 of the 54 patients was 33.1 years; the oldest patient was 70, the youngest 9; the average duration of the tumor in the 36 cases in which duration was noted was four years, the longest duration about twenty-eight years, and the shortest two months. Forty-six of the tumors were located on the upper extremities and 8 on the lower; 32 of the 46 were on the right upper extremity, 13 on the left; the location of one was not indicated. The fingers were affected in 35 cases, the palm of the hand in 7, and the thumb in 4. The index, the second, and the ring finger were each involved ten times, the little finger was involved four times; the location was not indicated in one case. Forty of the tumors were associated with the flexor tendons, 5 with the extensor tendons, and 1 with both flexor and extensor tendons. Four of the 8 tumors of the lower extremities were on the toes, 2 on the third, and 1 each on the first and second, involving equally the flexor and extensor tendons. Three were in the malleolar region and 1 was associated with the extensor tendons of the third and fourth metatarsal bones. Tourneux believes that the color of these extraperiosteal tumors is due to their excessive vascularity.

Stewart and Flint, in 1915, reviewed the literature; they found 9 cases published before 1913 which had not been included in Tourneux's



list, and 8 new cases, bringing the total up to 73, geographically distributed as follows: Germany 26, France 24, Italy 12, Great Britain 7, and Switzerland 4. To their total should now be added the case reported by Pybus in 1917, and one by Ely in 1918.

Each of Stewart's and Flint's 2 patients was twenty-seven years of age, one a male and one a female. The tumor in the first case was located on the ulnar aspect of the right thumb; it had appeared two or three years after injury to the thumb by a saw and had persisted for seven or eight years. At operation the tumor was found to be attached by a pedicle to the tendon sheath of the flexor longus pollicis. In the second case the tumor was located on the flexor aspect of the joint of the left wrist. Two and one half years before examination the patient fell and injured the wrist which swelled and became discolored. A short time afterwards a small tumor made its appearance and gradually increased in size. It was removed in October, 1911. In January, 1915 the patient had a sound and useful hand with no recurrence.

It is obvious that the various authors quoted do not agree with regard to the true nature of this tumor.

Seventeen cases of benign xanthic extraperiosteal tumors of the extremities containing foreign body giant cells have been examined in the Mayo Clinic. Brief histories of the tumors are tabulated as follows:

#### AGE AND SEX OF PATIENTS

Total number of patients.....	17
Females.....	11
Males.....	6
Average age.....	47.2 years
Oldest.....	65 years
Youngest.....	21 years

#### LOCATION

Upper extremities.....	10
Right index finger.....	3
Right ring finger.....	2
Right little finger.....	1
Right second finger.....	1
Right thumb.....	1
Left index finger.....	1
Left wrist.....	1

Lower extremities.....	7
Right ankle.....	3
Right foot.....	1
Right second toe.....	1
Right leg.....	1
Left little toe.....	1

#### LESIONS

History of injury.....	6
History of infection.....	2
Average duration of lesion.....	7.6 years
Longest duration of lesion.....	24 years
Shortest duration of lesion.....	8 months
Average largest diameter.....	2.8 cm.
Largest diameter.....	8.7 cm.
Smallest diameter.....	0.5 cm.

#### TREATMENT

Local excision of tumor.....	12
Local excision and cautery.....	2
Amputation of toe.....	2
Amputation of finger.....	1

#### ULTIMATE RESULTS

Number of patients traced.....	15
Number living.....	14
Number dead.....	1
Recurrence.....	0
Average period of time since operation.....	3.5 years
Longest period of time since operation.....	8.4 years
Shortest period of time since operation.....	0.24 years

The patient reported dead, according to a relative, died from general decline at the age of 73. There had been no recurrence of the tumor more than seven years after local excision.

One patient's leg was amputated three months after he left the clinic by his home physician, because the tumor had been diagnosed sarcoma and because the wound following local excision of the tumor failed to heal. The x-ray examination made at the clinic had showed some bone destruction. Seven years after amputation, however, there is no recurrence.

#### MACROSCOPIC FINDINGS

Macroscopically the tumor appears as an encapsulated greyish or brownish or pinkish yellow lobulated mass. Whitish streaks of fibrous tissue connected with the capsule may be seen between the

yellow areas. The tumor is of rather firm and tough consistency. It differs from the foreign body giant-cell tumor of the bone marrow and of the gum in that the latter tends toward a reddish tinge, closely resembling the color of grape juice, and in its tougher texture. Some of the foreign body giant-cell tumors of the bone marrow, however, are exactly like the yellow extraperiosteal tumors. A number of authors believe that the type of tumor I am discussing originates in the tendon sheath; as a matter of fact, 16 of the 17 tumors of this series were intimately connected either with the tendon sheath or with the tendon; one tumor, however, was located between the skin and superficial fascia of the anterior aspect of the leg, about midway between the ankle and the knee. The tumors varied from 0.5 cm. to 8.7 cm. in diameter (Plate III, and Figs. 404, 405, and 406).

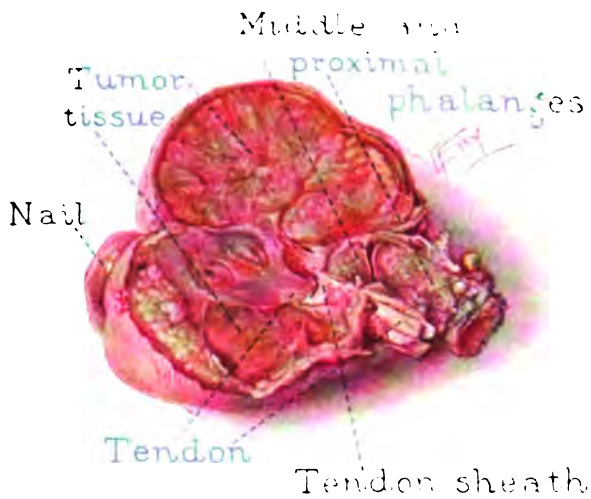
#### MICROSCOPIC FINDINGS

Microscopically the xanthic tumor is divided into fibrous and cellular areas. Fibrous bands surround the cellular areas, dividing the tumor into lobules. In some of the tumors the fibrous areas form the bulk of tumor substance and in others the cellular areas predominate. Bands of fibrous tissue may extend into the cellular areas. The fibrous areas contain a few cells of various descriptions.

In the cellular areas are small lymphocytes, fibroblasts, and a large number of medium sized cells with round and oval pale staining nuclei and very small nucleoli, probably endothelial cells. Some fields show a fairly large number of mononuclear phagocytes containing pigment and débris. Polymorphonuclear neutrophils and mitotic figures are very scarce.

All the tumors contain typical foreign body giant cells. In part of the tumors the giant cells reach as high as forty to the low power microscopic field, while in other areas of the same tumor only a few scattered cells can be seen. A few of the tumors show only a few scattered giant cells in any microscopic field. Some of these cells contain a small number of nuclei, while in others as many as 100 have been counted. The nuclei, on the average, are slightly larger than the small lymphocytes and are round or oval with a fairly regular outline containing small nucleoli. They lie in an eosinophilic protoplasm and bear a striking resemblance to endothelial cells. Some of the giant cells are lying in apposition to blood pigment, while others are in direct contact with the surrounding cells or lie in open spaces.

PLATE III



Case 181,833. Drawing of xanthic tumor of the second toe, showing the characteristic color and the close relationship of the tumor to the tendon and tendon sheath.





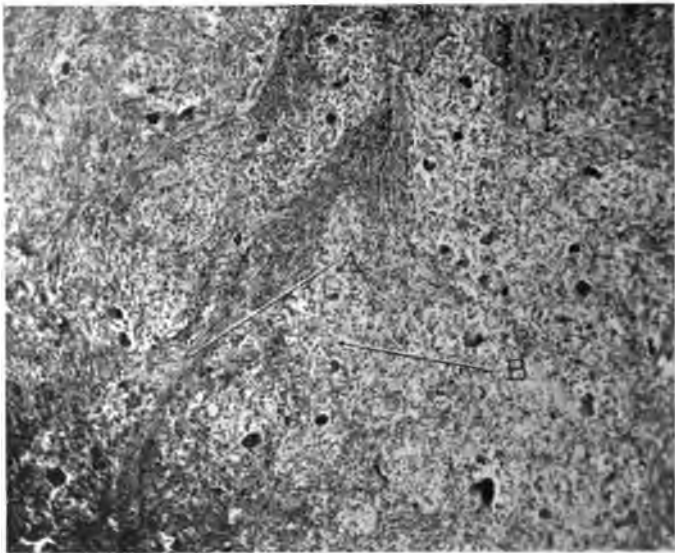
FIG. 404 (Case 62650).—Photograph of xanthic tumor on the anterior surface of the ankle



FIG. 405 (Case 107343).—Photograph of xanthic tumor of the right ring finger, showing close relation of the tumor to the tendon and the tendon sheath. (A) tendon, (B) tumor, (C) tendon sheath.



**FIG. 406** (Case 269555).—Photograph of xanthic tumor of the anterior surface of the leg, between the skin and the superficial fascia.



**FIG. 407** (Case 181833).—Photomicrograph of xanthic tumor of the second toe, showing fibrous and cellular areas with numerous foreign body giant cells. (A) fibrous area, (B) cellular area. Specimen from tumor shown in Plate III.  $\times 50$ .

These giant cells are like those found in the medullary giant-cell tumor of bone and of the gum, and like the giant cells that collect around cholesterol crystals, blood pigment, non-absorbable suture material, colloid, and cornified epithelium in cases of epithelioma, and like the giant cells that are associated with syphilis, leprosy, blastomycosis, coccidioid granuloma, and tuberculosis. In the latter two conditions

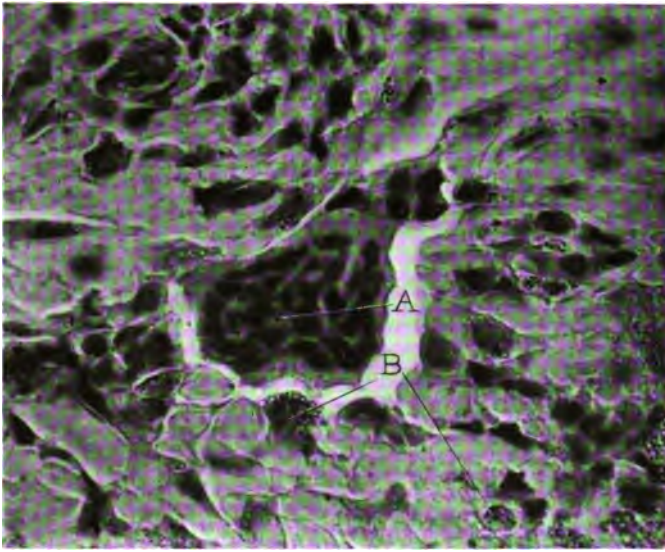


FIG. 408 (Case 69382).—Photomicrograph of xanthic tumor showing a typical foreign-body giant cell surrounded by fibroblasts, fibrous tissue, and phagocytes. (A) giant cell, (B) phagocytes.  $\times 500$ .

a number of the giant cells have peripherally arranged nuclei. The giant cells that are found in this tumor are also like the osteoclasts of normal bone.

Blood vessels are rather numerous in different parts of the tumors, also blood spaces. Foamy, lipid, or xanthoma cells are located mostly toward the periphery of the tumors, although a few can be seen in the center. All the tumors contain lipoids demonstrated by staining with Scharlach R and by Ciaccio's method, some in large amounts, while in others very little may be seen. Only one showed cholesterol crystals and all showed a positive reaction to iron (Figs. 407 to 425).



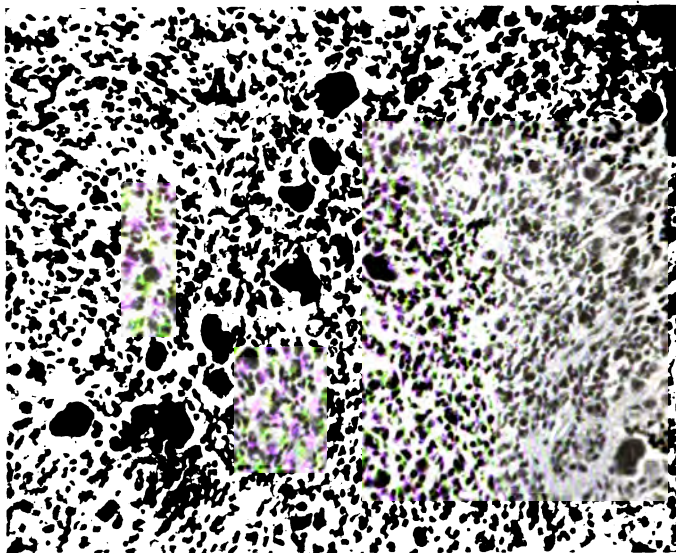


FIG. 409 (Case 225403).—Photomicrograph of xanthic tumor with a number of foreign-body giant cells.  $\times 100$ .

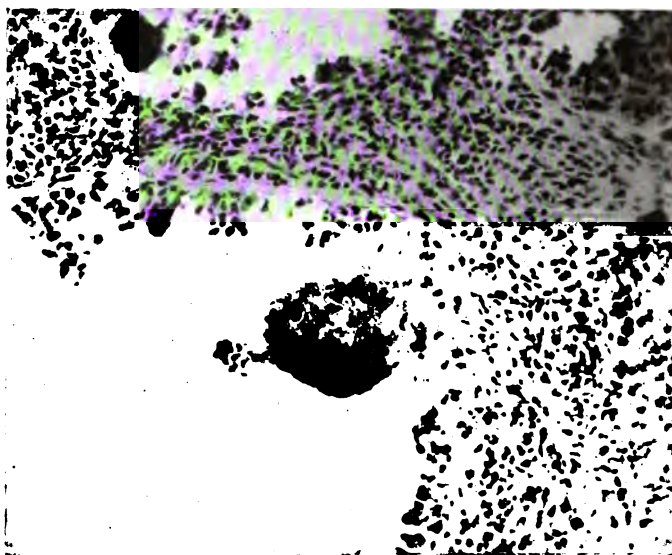
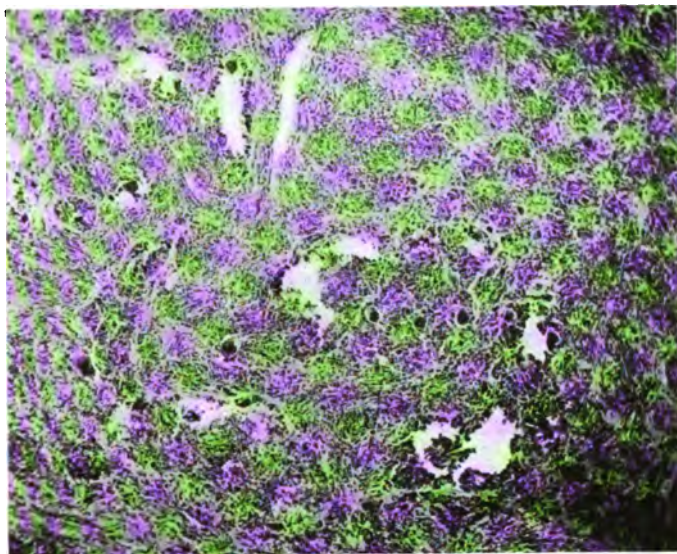
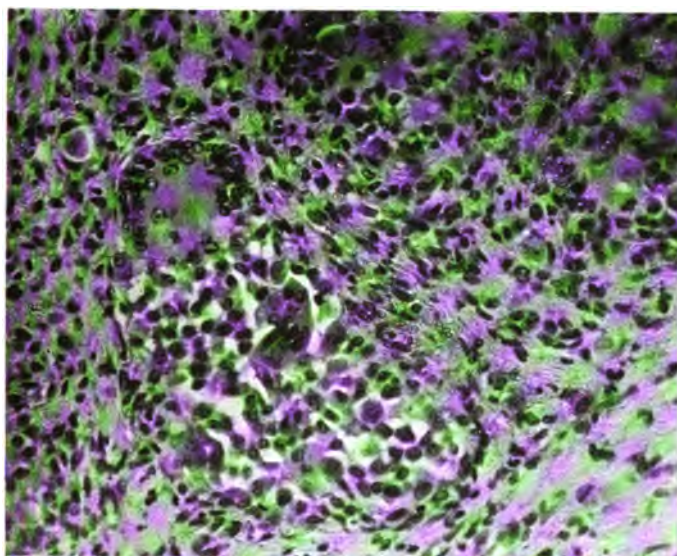


FIG. 410 (Case 69382).—Photomicrograph of xanthic tumor; foreign-body giant cell absorbing blood pigment in an alveolar space.  $\times 120$ .



**FIG. 411** (Case 69382).—Photomicrograph of xanthic tumor showing alveolar spaces and foreign-body giant cells.  $\times 50$ .



**FIG. 412** (Case 174019).—Photomicrograph of xanthic tumor; endothelial cell proliferation and foreign-body giant cells in alveolar space.  $\times 180$ .

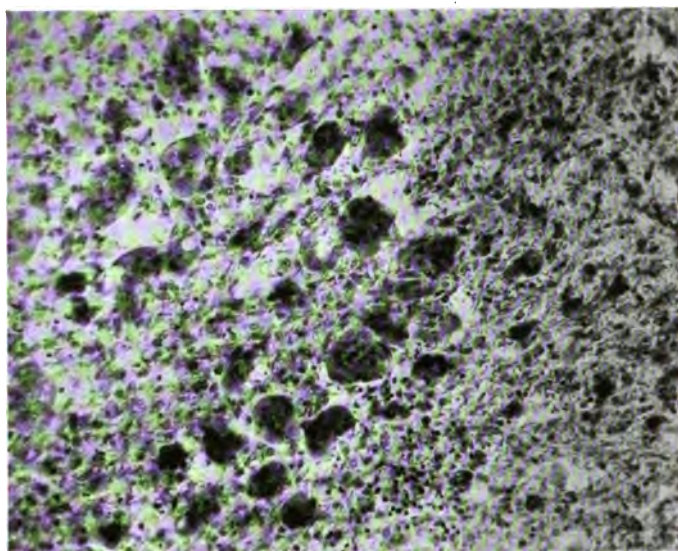


FIG. 413 (Case 202110).—Photomicrograph of medullary giant cell tumor of the tibia showing numerous foreign-body giant cells.  $\times 100$ .

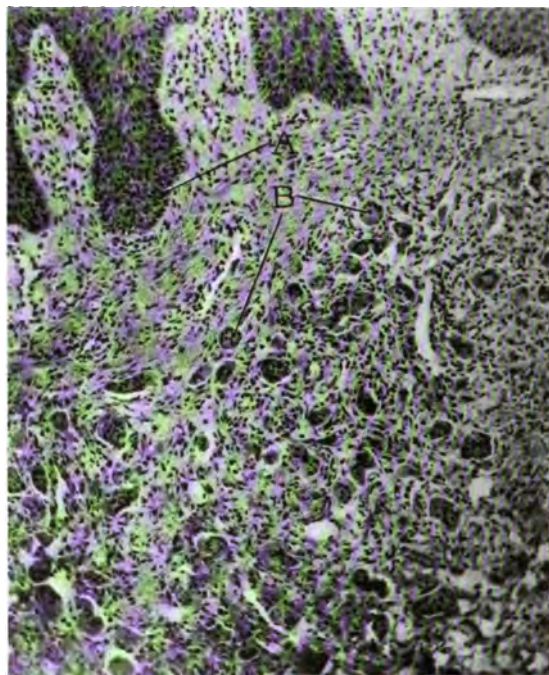


FIG. 414 (Case 186283).—Photomicrograph of giant cell tumor of the gum (epulis). (A) epithelium, (B) foreign-body giant cells.  $\times 70$ .



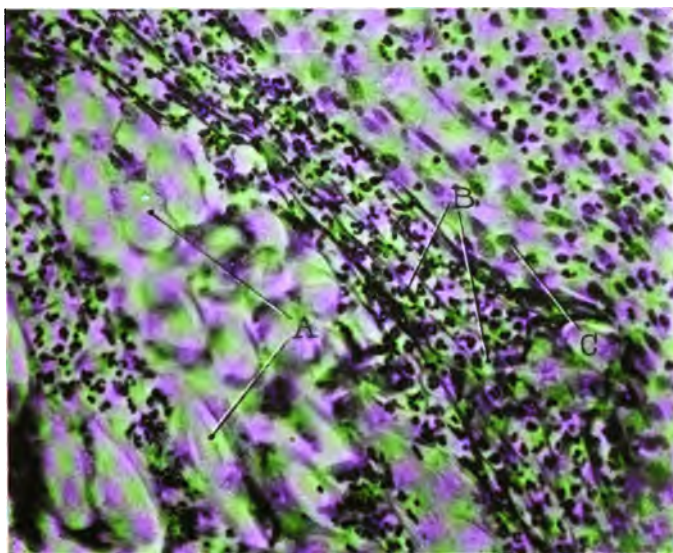


FIG. 415 (Case 260329).—Photomicrograph of non-absorbable suture material in gastroduodenal ulcer. (A) non-absorbable suture material, (B) polymorphonuclear leukocytes, (C) endothelial leukocytes.  $\times 200$ .

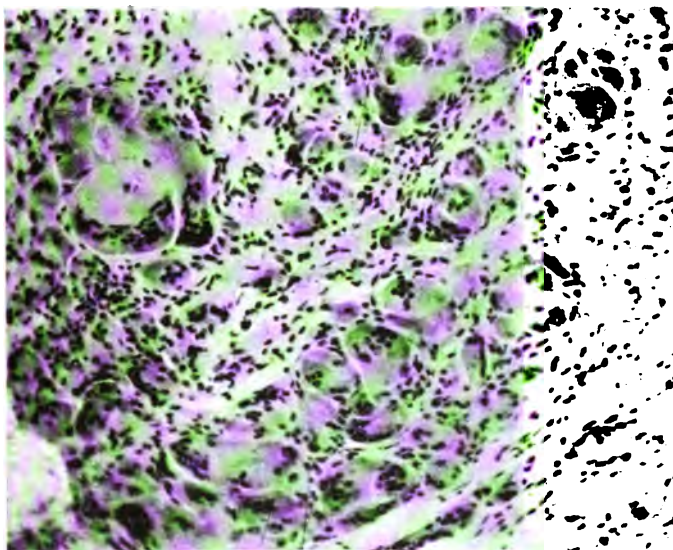
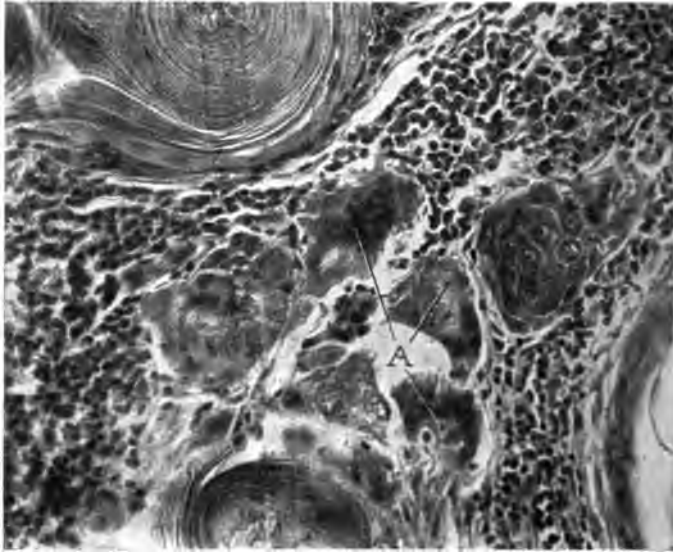
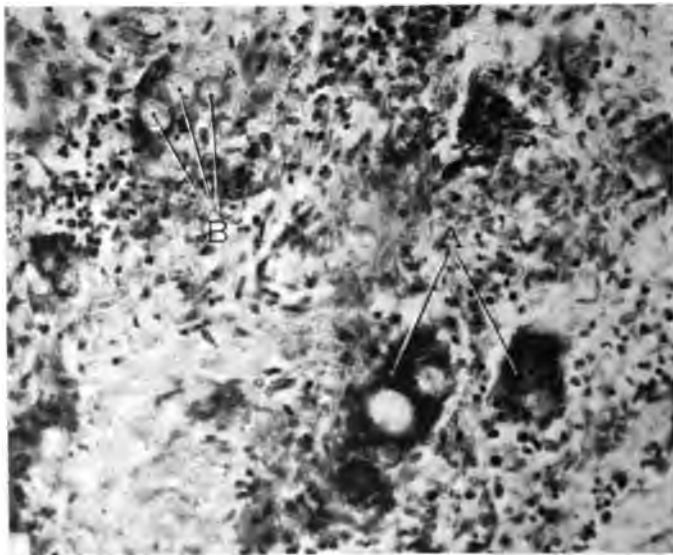


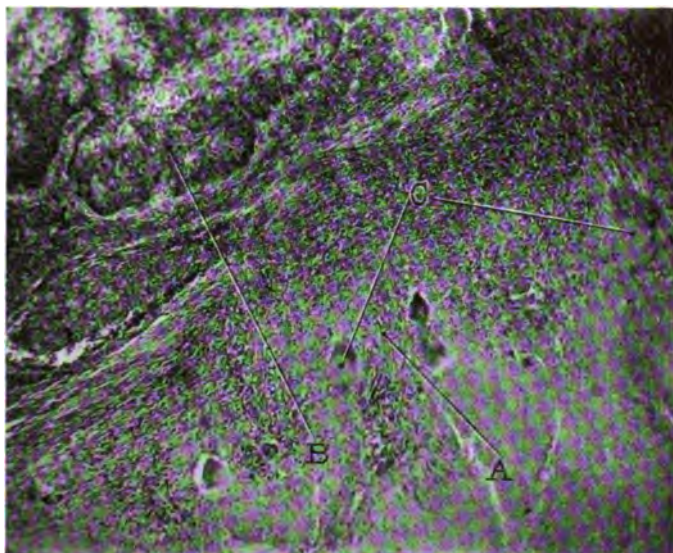
FIG. 416 (Case 260329).—Photomicrograph of foreign body giant cells near non-absorbable suture material in a gastroduodenal ulcer. Same specimen as shown in Fig. 415; different field.  $\times 100$ .



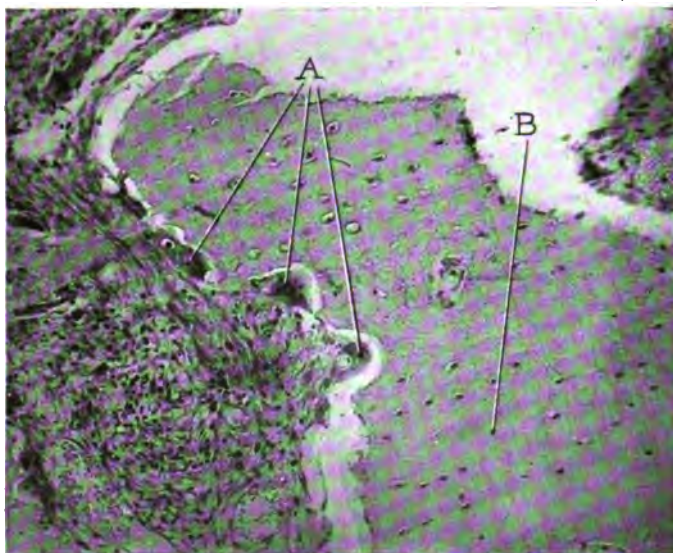
**FIG. 417 (Case 56099).—Photomicrograph of foreign-body giant cells absorbing cornified epithelium in an epithelioma of a lymph gland.  $\times 200$ .**



**FIG. 418—Photomicrograph showing foreign-body giant cells in a case of *coccidioides immitis*. (A) giant cells containing coccidioides, (B) coccidioides.  $\times 200$ .**



**FIG. 419 (Case 59139).—**Photomicrograph of tuberculosis associated with epithelioma, showing foreign body cells. (A) tuberculosis, (B) epithelioma, (C) giant cells.  $\times 50$ .



**FIG. 420 (Case 219836).—**Photomicrograph of (A) osteoclasts or giant cells absorbing the bone, (B) bone.  $\times 100$ .

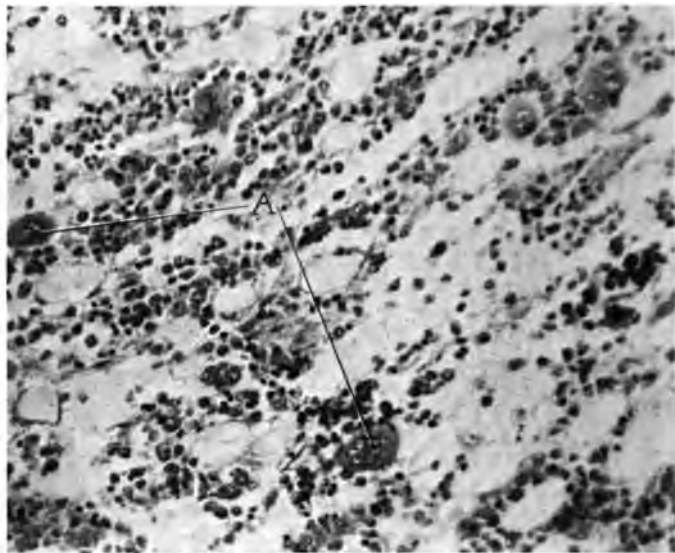


FIG. 421.—Photomicrograph of bone marrow; (A) osteoclasts or giant cells.  $\times 50$ .

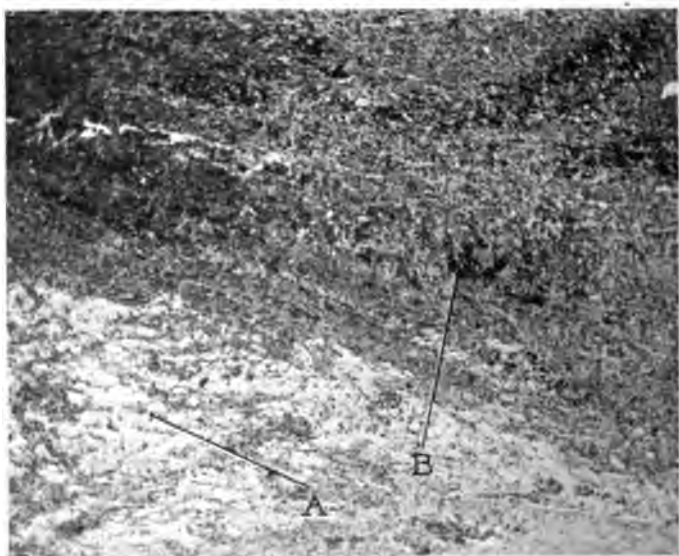
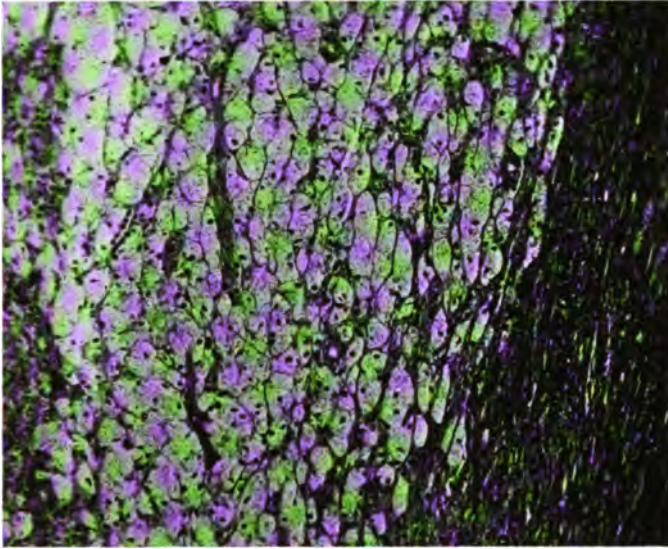
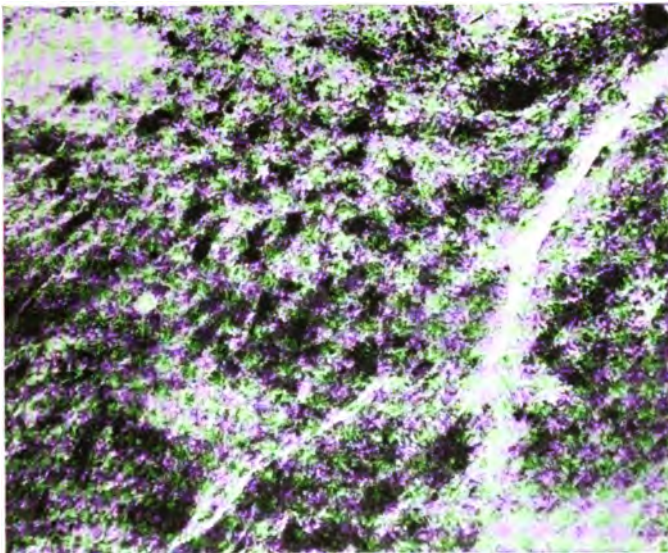


FIG. 422 (Case 74057).—Photomicrograph of xanthic tumor showing (A) xanthoma or foamy cells, (B) blood pigment.  $\times 50$ .



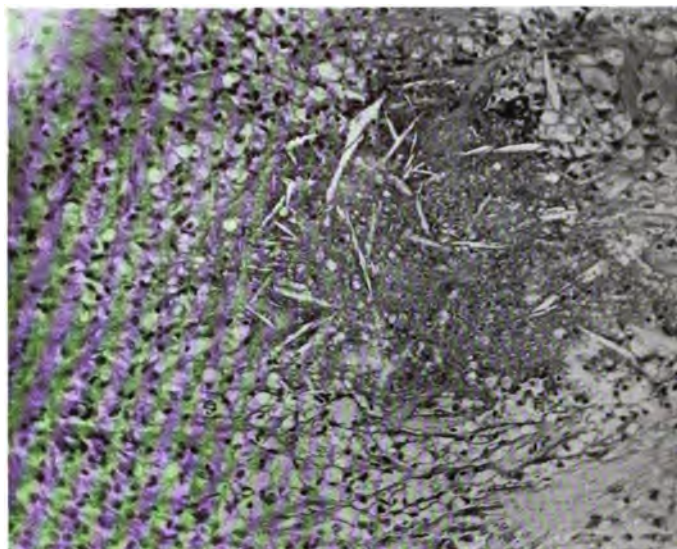


**FIG. 423** (Case 62650).—Photomicrograph of xanthic tumor showing xanthoma or foamy cells.  $\times 100$ .

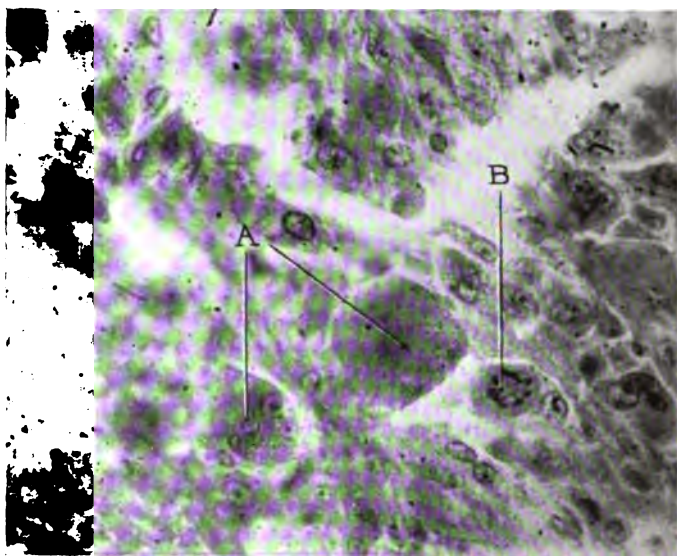


**FIG. 424** (Case 117155).—Photomicrograph of xanthic tumor showing lipoids, represented by the dark areas.  $\times 100$ .





**FIG. 425** (Case 62650).—Photomicrograph of xanthic tumor showing cholesterol crystals surrounded by xanthoma lipoid or foamy cells.  $\times 100$ .



**FIG. 426** (Case 76189).—Photomicrograph of medullary sarcoma of the tibia containing tumor giant cells. (A) tumor giant cells, (B) mitotic figure.  $\times 500$ .

## DISCUSSION

In a consideration of xanthic tumors attention must be paid to the significance of the microscopic architecture from a physiologic standpoint. A striking feature noticed under the microscope is the presence of foreign body giant cells. MacCallum in discussing their origin states that Maximow, "by the use of porous foreign bodies embedded in the tissues showed that lymphocytes which had wandered out from the blood vessels appeared as it were in pure culture in the spaces of the foreign body, and subsequently grew and developed until, in their various stages, they became identical with all the forms of large mononuclear wandering cells with abundant protoplasm and phagocytic activity. . . . Fusion of several such cells produces giant syncytium like cells with many nuclei which are particularly able to engulf foreign bodies and are known as foreign body giant cells."

Mallory believes that the foreign body giant cells are formed by fusion of endothelial leukocytes. Of the origin of endothelial leukocytes, he says in his text book, "They are derived from the endothelial cells lining blood, and to a less extent lymph, vessels by proliferation and desquamation. They also multiply by mitosis after emigration from the vessels into the lesions." Mallory's conclusions in an article on giant-cell sarcoma are:

"Giant cells of at least two different types occur in tumors. One type results in multiple mitosis and is a true tumor giant cell. It signifies rapid growth and may occur in a variety of different tumors.

"The second type is due to endothelial leucocytes invading tumors, especially those involving bone, and fusing to form foreign body giant cells. They are not tumor cells (although the tumors containing them are the ones which receive the name of giant cell sarcoma) and usually signify only erosion and disintegration of bone. Tumors containing these giant cells should be classified according to the nature of the type cell from which they arise. The term giant-cell sarcoma should be discontinued."

Alveolar spaces are seen in the cellular areas filled with the various kinds of cells I have described; these spaces show definite endothelial proliferation which makes them appear like blood sinuses. Blood pigment may be seen in these spaces as well as being scattered in patches throughout practically the whole of all of the tumors.

We know that the foreign body giant cell has a definite purpose in

the tumor, namely, to absorb foreign material. This material may be blood pigment, cholesterin crystals, and other foreign substances. It is a well known fact that the function of the osteoclast is to absorb bone, calcified cartilage, or anything that needs to be cleaned up, in other words, it is a "clean-up cell." Morphologically the foreign body giant cell is like the osteoclast; since they are morphologically the same, the chances are that their functions are similar.

Before a new house can be constructed where an old one stands, the old one must first be burned or moved away whole or in parts. A similar process takes place in bone construction; the osteoclasts tear down and clean up and make way for the osteoblasts which are bone builders. All the normal cells of the normal organism have a definite function; not to know their function is ignorance on our part.

We have every reason to believe that it is the function of the foreign body giant cell to absorb foreign material, which is not only found in this tumor but in great numbers in the medullary giant-cell tumor of bones, and also in the giant-cell tumor of the gum. It is sometimes found in malignant tumors. It is called on to perform its function in various parts of the body and because it looks like an osteoclast one must not assume that it is connected with bone, since it is found in places far removed from bone tissue.

The true tumor giant cell differs from the foreign body giant cell by having large irregular nuclei and often a mitotic figure (Fig. 426). The nature of the tumor must be judged by other cells and not by the foreign body giant cells (Fig. 427). One of the tumors in our series was rather extensive and had become attached to the tibia, fibula, and astragalus, causing some destruction of bone. The tumor was excised but the wound did not heal and the leg was amputated elsewhere three months later. This tumor caused the destruction of bone because it contained a large number of foreign body giant cells that were performing their normal function of destroying bone. Because a tumor containing foreign body giant cells destroys bone does not necessarily mean that the tumor is malignant. The same process takes place in the medullary giant-cell tumor of bone and in the giant-cell tumor of the gum.

Large mononuclear phagocytes are seen in a number of the microscopic fields. Foamy cells which are filled with a lipoid substance are present in 64.7 per cent of the cases. Blood pigment is in evidence in almost every microscopic field. These findings naturally suggest that the process is a degenerative one. On the other hand, fibroblasts

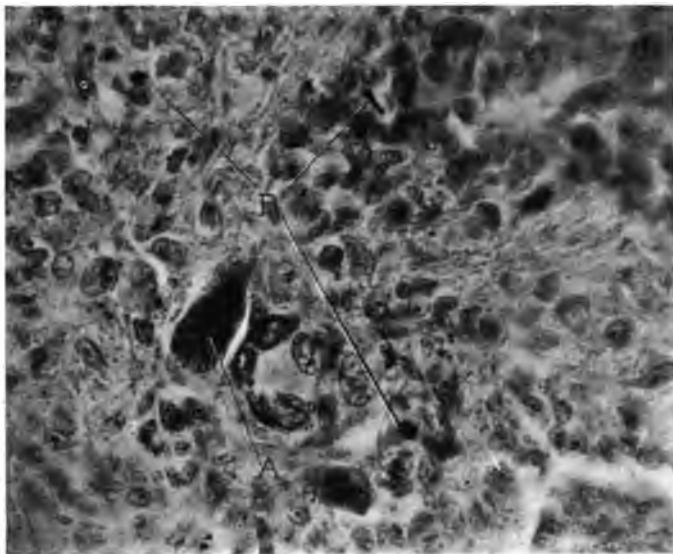


FIG. 427 (Case 275800).—Photomicrograph of a rapidly growing medullary sarcoma of the femur containing foreign-body giant cells. (A) foreign-body giant cell, (B) mitotic figures.  $\times 200$ .

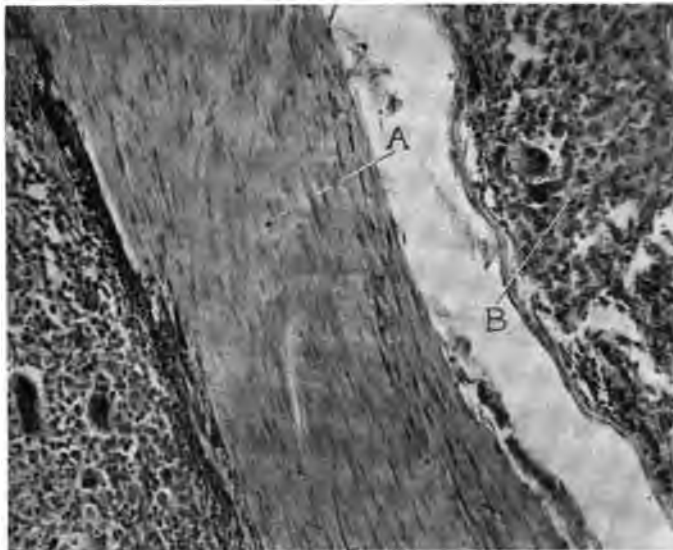


FIG. 428 (Case 181836).—Photomicrograph of a xanthic tumor intimately connected with the tendon, (A) tendon, (B) tumor.  $\times 100$ .

with an abundance of fibrous tissue are quite numerous. In some fields blood vessels as well as alveolar blood spaces are fairly numerous, the latter showing a marked endothelial proliferation. Cells that look like endothelial cells are quite numerous in all the cellular areas. Lymphocytes are frequently found in the fibrous tissue and in the cellular areas. When these facts are taken into consideration, the natural conclusion is that a constructive process is going on.

Injury seems to play an important part in the origin of xanthic tumors; 35.3 per cent of our series of patients gave a definite history of injury. In two of the cases, the finger was cut and the growth started shortly afterward. In one the second toe swelled after a horse had stepped on the foot. In the case in which the leg was amputated elsewhere, a horse had fallen on the ankle, and the swelling which appeared remained permanently. Infection must also be considered a factor as it may be possible that the tumor starts as the result of the extravasation of blood into the tissues, caused either by infection or by injury. Evidence of old hemorrhage is one of the constant findings.

The microscopic findings in bursitis and chronic tenosynovitis are similar to the findings in the xanthic extraperiosteal tumor, except that giant cells are only occasionally seen in the two former conditions in which the foamy or xanthoma cells, endothelial proliferation, fibroblasts, and blood pigment are also found. Foamy cells are likewise present in some hemangiomas. Most writers believe that the xanthic tumor starts from the tendon sheath, but in one of our cases it was located between the skin and superficial fascia; all the others, however, were in close relationship to tendons (Fig. 428).

Bloodgood in a recent article on medullary giant-cell tumor of the lower end of the ulna, said: "The more I study this group of local growths, the more convinced do I become that it belongs to a special type of angioma or granulation tissue tumor of which the xanthoma is a variety." He further states that, "The majority of tumors about the tendon sheaths contain giant cells and the stroma is not unlike the central giant-cell tumor of bone . . . . These tendon sheath tumors seem to have a distinct relation to trauma."

While the type of tumor under discussion has been pronounced malignant by some writers, it is regarded as benign by others. Fleissig called it a granuloma while Dunn expressed the view that it is on the border line between tumor growth and granulomatous formation.

It may be concluded, therefore, after thorough macroscopic and microscopic examination of seventeen of these tumors, and a consideration of the clinical history and ultimate result, that it is justifiable to call them benign growths, which are probably the result of the extravasation of blood following injury or infection, as they seem to have more of the microscopic features of a granulation tissue tumor than of a true neoplasm. Under no consideration should they be called sarcomas.

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## CHONDROMAS\*

H. W. MEYERDING

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Among the bone tumors that tax the diagnostic ability of clinician and surgeon are the cartilaginous tumor which, though non-malignant may suddenly assume aspects of such rapid growth as to lead to an alarming prognosis and to unwarranted surgical intervention. Even with careful history-taking and the accumulation of clinical, laboratory, and x-ray findings the diagnosis may remain obscure until surgical measures permit a pathologic study of the cellular activity in the tumor-mass.

The material discussed in this paper represents the proved cases, both pathologically and surgically, of chondromas that have been observed in the Mayo Clinic within the past seven years. Osteochondromas, chondrosarcomas, and so forth, will not be considered.

Enchondromas and echondromas are usually composed of hyaline cartilage supported on a fine framework of fibrinous connective material with remarkably little vascularity. Occasionally irregular bony deposit trabeculations are found. The enchondromas arise from some area not normally associated with cartilage while the echondromas arise from sites of preexisting cartilage and are possibly more of a hyperplastic tumor formation.

To rickets, trauma, displaced embryonal rests, syphilis, and a transition of connective tissue cells has been ascribed the cause of chondromas. The last cause appears the most reasonable because of the presence of cartilage and tumor-formation in various organs. The exciting cause, however, may not be apparent; it may depend on a variety or a combination of causes. In my own experience trauma has very often been a preexisting factor in the production of such tumors. They occur frequently before the age of puberty and even in the new born. In the cases under discussion the tumor appeared comparatively late, but the history often led back many years before the growth was first noticed.

\* Reprinted from Jour. Orthop. Surg., 1923, ii, 77-91.

Chondromas may be single or multiple. They may arise in and about joints and cause loose bodies, and so forth. The symptomatology varies. It is dependent somewhat on the location, size, and condition of the tumor-substance. Thus a tumor may feel hard in the early stage, and later present a palpable surface not unlike a cyst or a bursa, due to the mucoid degeneration which is almost sure to occur in the later stages, or a superimposed bursa may arise from repeated irritations. As a rule the chondromas are hard, lobulated, firmly attached, painless masses, not adherent to the skin. They may cause aching and tenderness if they are large and make pressure on sensitive structures. In long standing cases with the formation of tumors, shortening or fracture may occur. In the area of the tumor there is an absence of enlarged veins so often found in the region of malignant neoplasms of the osseous system. Local heat is absent unless there is degeneration and secondary infection; pulsation is absent. The x-ray pictures are not always characteristic.

Fibrocystic disease, giant-cell tumors, and more rarely, malignant bone tumors and osteomyelitis may produce shadows resembling chondroma so closely that the true nature of the tumor is not recognized until operation is done and a pathologic specimen is examined. The x-ray alone may not give sufficient evidence on which to make a diagnosis; however, it is of great value in that it determines readily the extent of involvement and the differentiation of the single and multiple types. The common use of the x-ray in fracture work in the future will undoubtedly reveal the presence of chondromas and other bone tumors with increasing frequency. Surgeons should not overestimate their ability to read the x-ray plates. Very often bone tumors are interpreted as malignant when careful history-taking and clinical examination might have led to a more guarded prognosis and to more conservative surgery. A study of the roentgenograms in these cases leads one to divide chondromas into two groups:

Group I, in which the bone presents oval, transparent areas with edges clearly marked out from the surrounding bony structure. The area usually involves the medullary substance near the epiphysis and slowly thins or compresses the cortex by bulging it outward, forming round or lobulated masses without breaking through the periosteum or invading the soft tissues.

Group II, in which many irregular, ramifying, homogeneous areas of various sizes and shapes are separated by lines of various thicknesses



and directions, and by coarser lines due to the shadows thrown by the bone trabeculations. The areas show the absence of periosteal involvement or a tendency to invade the soft tissues. They also show a tendency to invade the cortex rather than to bulge it out or to cause its absorption from pressure. Calcification or ossification may occur and will be noted by their characteristic appearance.

It was noted in many of our cases that chondroma tends to arise near or in the epiphyseal line and to invade the epiphysis as well as the diaphysis. This causes a picture resembling that of giant-cell tumors, yet it is often apparent that the striations and trabeculations are coarser and that the shadows are deeper in chondromas. As I have noted,<sup>1</sup> in the cases reported as cystic and fibrocystic disease of the long bones, there is an absence of the epiphyseal involvement. This distinguishing feature of fibrocystic, giant-cell tumors, and the heavy and coarse trabeculations characteristic of chondromas would indicate that the two might be differentiated roentgenographically. It should be remembered, however, that the x-ray cannot disclose the exact nature of cell activity. A tumor may have the appearance of a benign growth yet some portions of the mass may be malignant. During the early stages this will not be manifested by the x-ray although later the condition may be accurately diagnosed from the plate alone.

Preoperative laboratory tests, in our experience, have been of little value other than negative in making a diagnosis. The Wassermann tests have been negative, and urinalyses have shown the presence of albumin in a few cases. In one case of multiple chondroma Bence-Jones protein was noted.

#### TREATMENT

Chondromas should be treated surgically and the earlier the operation is done the better the prognosis. Incision and curettage are usually sufficient to produce a cure unless the tumor has become large or is likely to interfere with joint action. In such cases radical measures may be indicated. If the tumor bulges into the soft tissues, it may be wise, after curettage, to crush the wall and allow the cavity to be closed by newly formed bone. This also reduces the deformity.

At operation an encapsulated, firmly adherent, hard tumor with or without a superimposed bursa presents itself. On opening the

thin cortex the tumor may be shelled or curetted out with surprisingly little hemorrhage. The mass is a pale, bluish-gray, fragile tissue which on section is shown to be hyaline cartilage. No packing is required, and the cavity may be allowed to fill with blood clot or a fat transplant may be used. If the bone is thin to an extent that would make fracture imminent, a cast or splint should be applied.

The prognosis following operation is good. Occasionally the tumor may recur or, more rarely may become malignant. Sections from various parts of the tumor should be examined, especially those parts exposed to repeated trauma, since in them malignant changes are most likely to be found. Varying amounts of cartilage may be present in the malignant tumors. The tissue, therefore, should be studied histologically, for the gross appearance may deceive the surgeon and a prompt recurrence both locally and generally would soon show the true nature of the growth.

#### REPORT OF CASES

Case 1.—W. A., a boy, aged 15, came to the clinic for examination March, 1910, complaining of a tumor of the left great toe. The toe was painful and tender. The patient's home physician had excised a portion of the tumor for "proud flesh" and had trimmed the nail which grew at right angles to its normal position. The formation of the tumor was ascribed to an injury to the toe eighteen months before. The examination at the clinic was negative except for the presence of a firm, apparently cartilaginous mass under the inner border of the left great toe. This was excised under a general anesthetic, and on pathologic examination was found to be a chondroma. One year later the patient returned with a recurrence. A second pathologic examination again showed the condition to be chondroma. Seven years later in answer to a letter of inquiry the patient states that he is an officer in the army, that he has had no further recurrence and is in excellent health. (Note: This chondroma apparently resulted from an injury, was of slow growth, and was successfully treated by conservative surgery.)

Case 2.—T. F. S., a man, aged 40, was operated on in March, 1913, for ulcer of the duodenum. A posterior gastro-enterostomy was done. At this time also a tumor of the left thumb was excised and found to be a chondroma. The tumor had been growing slowly for three years. Six years later the patient stated that his health was excellent. He had gained sixty pounds in weight, but a swelling had appeared at the site of the excision of the chondroma within a year after the operation.

Case 3.—E. L., a girl, aged 7, was examined June, 1913. Two years before, the patient had had a severe attack of fever which had confined her to bed for three months. During this time it was noted that tumors were forming on her right hand. They grew slowly the first year, but during the second year they increased rapidly in size and caused pain and tenderness, particularly just before a storm. The clinical examination showed several tumors of the fifth metacarpal, one on each of the proximal phalanges of the fourth and fifth fingers of the right hand. There was no sign of in-

flammation and no tenderness. The Wassermann test was negative. The tumors were curetted and cauterized with the actual cautery, and iodoform gauze packs were inserted. Pathologic examination showed the growths to be chondromas. The patient was examined four months later, clinically and by the x-ray; she showed marked improvement except for a slight recurrence on the fifth finger which required similar treatment. Five years later the patient stated that her health was excellent and that she had had no definite recurrence of the condition.

Case 4.—P. J., a girl, aged 9, came for examination August, 1913, because of a tumor on the right great toe which had formed following an injury four months before. A poultice had been applied to the inflamed toe with some relief, especially after the pus was drained. The toe, however, remained sore, and very soon afterward a tumor was noted which gradually increased in size and caused pain on walking or when touched. The mass had elevated the nail. An x-ray picture showed partial destruction of the distal phalanx. The tumor had been diagnosed a sarcoma, but operation and pathologic examination revealed chondroma. Five years later the patient reported "no recurrence and condition very satisfactory."

Case 5.—A. B. M., a woman, aged 45, was examined August, 1913. She complained of a recurring tumor of the little finger of the right hand, a tumor of the outer lower quadrant of the right breast, which had been present for twenty-two years and occasionally caused stinging pain, and a tumor of the right arm. At operation the right breast was amputated and the tumor found to be adenofibroma. The tumor of the arm was a lipoma, and the two tumors of the finger were chondromas.

Case 6.—P. C., a boy, aged 9, came to the clinic March, 1914, because of a tumor of the proximal phalanx of the little finger of the left hand. The growth had been slowly enlarging for one year, but it did not cause pain or discomfort. The x-ray showed a partial destruction of the phalanx. The material was curetted out and was found, pathologically, to be a chondroma. Four and one-half years later the patient reported that he was well and had had no recurrence.

Case 7.—B. K., a man, aged 25, was sent to the clinic in July, 1917, by his home physician because of a tumor of the fifth metacarpal bone of the left hand. The tumor had been present twelve years without symptoms. It had recently been injured and malignancy was feared. The examination disclosed a firm, hard tumor of the distal portion of the fifth metacarpal bone of the left hand. The x-ray picture showed a cystic area traversed by coarse, irregular trabeculations. The tumor bulged outward causing a thinning of the cortex without noticeable change in the periosteum or invasion of the soft tissues. At operation the curetted material, grossly and microscopically, resembled chondroma. The bulging section of the cortex was crushed in and the wound closed without drainage. Primary union occurred. No response was obtained from a letter of inquiry sent to this patient.

Case 8.—A. L., a man, aged 22, was referred for examination October, 1913, by his family physician because of a firm mass that had been noted in the region of the right lesser trochanter three months before, and which had been slowly enlarging and causing pain. Malignancy had been diagnosed. No definite history of trauma was given. Examination was negative except for the tumor, which caused an increase of 4 inches in the circumference of the thigh and hindered adduction. The patient was apparently in excellent health. There were no enlarged veins about the tumor and no tenderness. An x-ray diagnosis was made of sarcoma. The bony feel, however, and the lack of venous enlargement, the general good health of the patient, and the density of the tumor mass in the x-ray picture led to an exploration through an anterior incision. The tumor, which was removed, consisted of cartilage. Its base

was cauterized and a small strip of gauze was used as a drain. The convalescence was uneventful. Two months later the patient came for observation. X-ray of the chest and thigh failed to reveal any recurrence.

Case 9.—G. M. Z., a man, aged 38, was examined June, 1917. A tumor had been present for fifteen years on the middle phalanx of the second finger of the right hand. pain. The size had remained stationary for two years. The patient had had repeated



FIG. 429 (223429).—Chondroma of the epiphysis of the right femur; cyst at inner condyle. Chondromas of the outer condyle, and one just above the intracondylar notch; front view.

attacks of tonsillitis, and three weeks previous to examination septic tonsils had been removed. A diagnosis of chondroma was made from the x-ray and clinical findings and the duration of the growth. No operation was done.

Case 10.—J. A. S., a woman, aged 43, came for examination September, 1914, because of a tumor in the lower end of the sternum. The growth had been noticed five months before and had slowly increased in size, causing pain in the costal arches, especially of the left side. The patient was very uncomfortable while lying down and for the past three weeks had sat up all the time. She had lost strength and 10 pounds in weight and had a dry cough. Clinical examination revealed a firm, bony, slightly tender tumor of the ensiform  $1\frac{1}{2}$  inches in diameter. The x-ray of the chest was

negative. The tumor was excised and on pathologic examination was found to be cartilaginous. The patient returned three months later, complaining of pain in the sternum and chest through to the back. Her general health was good. The x-ray showed a dense mass in the right mediastinum. At operation a cartilaginous mass was found which involved the under surface of the sternum and extended upward into the pleura of the right lung so extensively that further dissection was deemed inadvisable. The material removed was pure cartilage. Eight months later the patient's husband reported that she was slowly failing.



FIG. 430.—Side view of chondroma shown in Fig. 429.

Case 11.—E. M., a man, aged 24, was examined January, 1915, because of tumors of the right hand which he had noticed one year previously. The growths did not cause marked pain or discomfort, but they were gradually enlarging. At the base of the first phalanx was a firm, painless, slightly movable tumor one-half inch in diameter. Between the second and third metacarpals were smaller tumors, and one extended over the palmar space of the second metacarpal. Operation revealed these tumors to be chondromas not connected with the bone.

Case 12.—H. H., a man, aged 22, came for examination March, 1915. He complained of a slowly growing painless tumor on the right scapula which he had noticed six months before. A hard, bony mass 2 by 3 inches was palpable at the superior

angle of the supraspinous fossa. The x-ray showed a calcified tumor of the scapula. On removal and pathologic examination it proved to be a calcified chondroma. Two years later the patient wrote asking for a statement for an insurance company. He said he was well. Three years afterward he was discharged from the army because of tuberculosis of the lungs. The tumor had not recurred.

Case 13.—H. R. H., a man, aged 50, was examined March, 1915. The patient had first noticed tumor of the right knee twelve years before; it had gradually increased in size. There was no pain or locking, but stiffness of the joint. A firm mass, apparently arising from the posterior surface of the tibia, was palpated in the right popliteal space. It was movable, and limited flexion to 90 degrees. The skin was scarred from previous treatments and heat. The Wassermann was negative.



FIG. 431 (226027).—Multiple chondromas of the hands.

The x-ray showed calcareous deposits in the popliteal space and marked bronchial thickening. The tumor was removed and the base cauterized. Gross and microscopic examinations showed it to be a chondroma. Three years later the patient reported that he was in good general health and that there was a small lump on the outer side of the knee, which had not enlarged in the past year.

Case 14.—N. R., a girl, aged 17, was examined September, 1915, for a tumor of the proximal phalanx of the little finger of the left hand. This finger had been caught in a door and the phalanx fractured when the patient was eighteen months old. Five years later a tumor formed, and after enlarging slowly for six years it remained stationary. The tumor limited motion of the finger and caused pain with movement. Examination revealed a hard, fixed tumor one-half inch in diameter at the base of the proximal phalanx. The x-ray picture showed a tumor bulging into the cortex but not involving the periosteum or perforating into the soft tissue. Its central portion was transparent and crossed by numerous coarse trabeculations. The tumor was curetted out and proved to be a chondroma. Two and one-half years later the patient wrote that there had been no recurrence.





FIG. 432.—X-ray of chondroma shown in Fig. 431 taken just before operation.



FIG. 433.—X-ray of chondroma shown in Figs. 431 and 432, taken six months after operation.

Case 15.—J. L., a man, aged 32, came for examination February, 1918. For the past two years the patient had noticed at night a dull pain in the right knee and occasionally in the left. There had been no disability and he had continued to work up to the time of his examination. Examination revealed slight tenderness over the inner side of the right knee and slight limitation of flexion. The x-ray showed cystic areas in the epiphysis of the femur without involvement of the periosteum or perforation into the soft tissue; it was multilocular with coarse trabeculations. At operation



FIG. 434 (168792).—Chondroma of the lower end of the femur. Note the involvement of both epiphysis and diaphysis and the extension to the knee joint but not into it. The periosteum is normal except at the point of exploration. Cortex and medullary bone are both involved with areas of lessened density while trabeculations are marked and coarse; front view.

a multiple lobulated, cartilaginous mass was removed. Beside the mass, just above the inner condyle there was a cystic cavity about an inch in diameter. The wound was closed after a thorough curettage. Pathologic examination showed chondroma. One year later the patient was in good health and without local recurrence (Figs. 429 and 430).

Case 16.—H. B., a man, aged 18, was examined January, 1918. At the age of two years the patient had developed a tumor of the proximal phalanx of the fifth finger of the right hand. There was no history of trauma. Within the last four years new tumors had formed on the metacarpals and phalanges of both hands. These grew at approximately the rate of body growth: they caused little discomfort and no pain unless traumatized. There was surprisingly little disability considering the size and



number of tumors. The patient was referred by his physician because of the deformity, and with the diagnosis of chondromas. Operation consisted of curettage of cartilaginous material and cauterization of the cavities. Six months later the patient showed marked improvement (Figs. 431, 432 and 433).

Case 17.—W. H. W., a man, aged 41, came for examination July, 1918, because of flat feet. When the patient was eighteen months old, his right hand had been crushed in a door, and following this tumors developed and grew until his nineteenth year. His physician had advised against surgery. He had worked steadily as a carpenter



FIG. 435.—Side view of chondroma shown in Fig. 434.

and had been inconvenienced only by limitation of flexion of the first finger. A diagnosis was made of multiple chondromas of the right hand. No operation was performed.

Case 18.—(168792.) J. B. W., a woman, aged 53, was examined August, 1916. The patient complained of nervous indigestion, insomnia, rheumatism, and lameness of the left knee. Lameness and stiffness had been present for seven years although there was no limitation of motion, no deformity, or tenderness. A diagnosis of sarcoma had been made elsewhere, and amputation had been advised. No definite enlargement of the knee nor limitation of motion was found. The urinalysis was negative; the hemoglobin was 80 per cent; the leukocytes, 5,200. The tonsils were enlarged and contained septic material. The x-ray showed the presence of a tumor in the lower end of the left femur (Figs. 434 and 435). Other x-ray findings were negative. August 18, 1916, the tumor was explored and found to be a chondroma. Radium was used. April 5, 1917, the tumor was curetted and the cavity filled with fat from the abdominal wall. The patient has continued to walk since her operation three and one-half years ago. No evidence of further growth can be found clinically or roentgenographically.

## SUMMARY

Chondromas usually occur at sites of preexisting cartilage, the epiphyseal line, and so forth, and involve the epiphysis and diaphysis. There is a greater tendency to growth into the epiphysis where, at times, the growth apparently remains until late in the history. The periosteum is not involved and appears normal by x-ray and at operation. The cortex may appear normal by x-ray and at operation unless it is thinned by pressure or bulges out, or unless it is involved with the medullary substance, when it appears as a homogeneous tumor.

Chondromas do not invade the soft periosseous tissues as is so frequently seen in malignant tumors. Trauma appears to be an etiologic factor, especially in the growths on the hands. Although these tumors occur most frequently in the young, they may occur late in life and should be taken into consideration when other factors indicate benign tumor formation. Superimposed bursæ may become injured, and a rapid swelling or a rapid growth may follow which is suggestive of malignant change or degeneration.

The contents of the tumor usually consist of pure hyaline cartilage in which a fine supporting framework of connective tissue is found, or it may be crossed by a bony network and trabeculations. The latter produce definite coarse lines in the x-ray picture which ramify in an irregular manner across the more transparent areas.

The history of the case, the clinical examination, and the x-ray findings may present such a complex picture that it will be necessary to resort to surgery and pathologic examination in order to arrive at a correct diagnosis. Even benign chondromas may recur, and such recurrences should be carefully watched for malignant change. None of the cases in this series showed subsequent malignancy. It should be remembered that degenerating processes may cause cysts, probably due to pressure-degeneration and poor vascular supply. The x-ray is of great value in determining the size, location, and difference between the single and multiple varieties of chondromas, but it should not be depended on in making a definite diagnosis. There was a fairly similar picture between the giant-cell tumor and the chondroma in some of our cases. Surgical intervention in cases of chondroma should be conservative. The prognosis is favorable.

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## A ROENTGENOLOGIC STUDY OF METASTATIC MALIGNANCY OF THE BONES\*

A. B. MOORE

Pfahler, in his excellent paper presented before this society in 1916, called attention to the characteristic roentgen appearance of metastatic carcinoma of the bone, and impressed on us the necessity of a thorough x-ray examination in all cases of known or suspected malignancy in which there is any suspicion of a secondary involvement in the osseous system. My object in this paper is further to emphasize this necessity and to give a summary of the combined clinical and roentgen findings in 65 such cases that have been observed in the Mayo Clinic.

Fraenkel, von Recklinghausen, and others, have described two types of secondary bone metastasis, the osteoclastic and the osteoplastic. The osteoclastic form is characterized by marked lacunar absorption and destruction of bone, causing an extreme porosis of the osseous tissue. The osteoplastic form is characterized also by lacunar absorption, but there is a marked thickening of the bone due to the collection of the malignant cells and a secondary calcification around the malignant process. According to these observers the two types occur simultaneously; this view is substantiated by the roentgenologic evidence, the two being found quite frequently in the same bone.

The osteoclastic form is characterized in the roentgenogram by an extreme decrease in density, the bone having a honey-combed appearance that is typical.

The osteoplastic form is characterized in the roentgenogram by an irregular increase in bone density, the bones having a chalky appearance without cortical or periosteal thickening. Our observations agree with those of Pfahler who states that the osteoplastic form is most common in cases of carcinoma of the prostate, while the osteo-

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clastic is most common as a secondary manifestation of breast malignancy. Authorities on the subject differ as to the route of extension; Handley doubts the extension by the blood stream and believes that the malignant cells metastasize entirely by way of the lymphatics. Risley, from his own studies and a review of the literature concludes that the metastasis occurs either by the blood or by the lymph stream.

The number of cases in our series in which there was no demonstrable involvement of either the deep or superficial lymph glands seems to show that the metastasis occurs quite frequently by way of the blood. von Recklinghausen states that the bone is primarily involved in its marrow and that the cortex is involved through the foramen.

Mathews believes that the most common sources of bone metastasis are the breast, thyroid, prostate, and kidney. In the present series the primary growth was situated as follows:

	Case
Breast.....	36
Prostate.....	11
Kidney.....	7
Thyroid.....	2
Vulva.....	1
Sigmoid.....	1
Uterus.....	1
Abdominal masses of unknown nature.....	3
Primary source not discovered.....	3

Carcinoma of the breast is unquestionably the most common primary source of bone metastasis, but if one considers the high percentage of carcinomas that are located in the breast the height of this percentage will be materially reduced.

There seems to be a wide disparity between our statistics and those quoted in the literature in which carcinoma of the thyroid is regarded as being second only to carcinoma of the breast as a source of bone metastasis. As I have stated, we have in this series but 2 cases of bone metastasis originating in the thyroid gland although we have seen several hundred malignant conditions of the thyroid, a high percentage of which were examined by the roentgen ray. This difference may be explained by Crotti's statement that malignant adenomas of the thyroid are very prone to give rise to bone metastasis, while it is very rare in cases of scirrhus cancer of the thyroid. The high percentage of metastasis that is secondary to malignancy of the

breast and prostate is probably due to the blood and lymph supply, and to the fact that the neoplasms are usually slow growing types.

In all probability the extreme rareness of bone metastasis in cases of cancer of the stomach is because malignant conditions of the stomach speedily produce death unless immediate treatment is given. In 1600 patients with cancer of the stomach who have been examined at the Mayo Clinic during the last ten years, no bone secondaries have been found. Of the 7 cases of bone metastasis secondary to tumors of the kidney, 6 followed hypernephromas, and one followed a so-called neurocytoma, a tumor originating in the sympathetic nerves in the adrenal. The case was that of a boy, aged 13, who had metastasis in the skull and sternum with a fatal termination within six months after the condition was discovered. In our experience the bony metastasis of all types of malignancy gives the same roentgen appearance, thus emphasizing the fallacy of attempting a cellular diagnosis by the roentgenogram. The metastasis in the present series was located as follows:

	Cases
Spine.....	22
Pelvis.....	11
Femur.....	9
Ribs.....	6
Humerus.....	6
Clavicle.....	1
Sternum.....	1
Radius.....	3
Skull.....	3
Tibia.....	2
Bones of hand.....	1

Risley states that metastasis is rare below the elbow and knee, and explains this by the fact that death usually occurs before the process extends. However, in our series were 6 cases; 3 in the radius, 2 in the tibia, and 1 in the bones of the hand, in which there was extensive involvement.

As Pfahler has noted, the spine is the most common site of bone metastasis and any vertebra from the atlas to the sacrum may be involved. In the 22 cases in our series showing spinal involvement more than one vertebra were involved in all and the process was located in the lumbar region in 75 per cent.

A review of the clinical histories of these cases shows that the average age of the patients was 50; 42 were females, and 23 were males; the average time that had elapsed since the primary growth was discovered was two and one-half years, the extremes being nine years in one case and six months in another. The most common symptom was pain, this being noted in 57 per cent of the cases. The pain is rather characteristic and resembles that of neuritis; it is almost always constant and is referred along the course of the nerve trunks. The pain is always increased by motion and the degree of the increase is in direct proportion to the proximity of a joint to the area involved. It has been remarkable that in spite of extensive areas of involvement, the patient was able to move without apparent inconvenience; this is especially true in cases with metastasis into the pelvic bones. While in cases of known or suspected malignancy the presence of pain should always be an indication for a thorough roentgen examination; it must be remembered that pain of a similar nature is a fairly common complaint of many patients over fifty years of age; this is particularly true in cases of extensive malignancy when pressure either from the primary growth or enlarged glands secondary to it, may produce pain. It should also be borne in mind that malignant metastasis to the spinal cord is not uncommon and that this produces pain similar to that caused by bone metastasis. Superficial swelling is uncommon in cases with bone metastasis, but in cases in which there is metastasis in the long bones or in the skull, irregularities may be discovered by careful palpation. As Boggs says, spontaneous fracture is a fairly common occurrence in cases of bone metastasis and may be the first index of its presence. Spontaneous fractures occurred in 6 of our 65 cases, and in 2 there had been no previous indication of malignancy. One of the spontaneous fractures, located in the middle third of the humerus, united without delay. Our statistics seem to show that pulmonary metastasis and bone metastasis rarely occur together; in but 3 of our cases was there any evidence of involvement in the lungs.

As I have stated, the roentgen appearance of bone metastasis is quite characteristic, and in most cases an unqualified diagnosis may be made. Of course in this, as in all conditions, the roentgen evidence must be corroborated by careful clinical history taking and examination. The cases presenting the most difficulty are those of suspected spinal involvement in which careful technic must be employed and satisfactory plates obtained before a diagnosis can be made. Lateral

roentgenograms, as described by Hickey, have proved a great aid in the examination of these cases.

#### CONCLUSIONS

1. Bone metastasis may result from malignancy of almost any organ, but the most common foci are the breast and prostate.
2. Bone metastasis is uncommon in malignancy of the thyroid.
3. Bone metastasis and pulmonary metastasis are rarely associated.
4. The most common symptom complained of is pain which is fairly typical and should be regarded as an indication for a roentgen examination.
5. The roentgen appearance is characteristic and a thorough examination should be made by the x-ray in all cases in which there is any suspicion of bone metastasis.

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## FRACTURES CONSIDERED AS POTENTIAL DEFORMITIES\*

M. S. HENDERSON

Every fracture has within itself the tendency to leave varying degrees of deformity and disability in its wake; any fracture should, therefore, be regarded as a potential deformity. The fact that the treatment afforded fractures as a whole usually gives good functional results indicates that the mechanical principles underlying the treatment are quite simple. In certain types of fractures, particularly those in the vicinity of joints, deformities are especially prone to occur. These deformities are seen with such frequency in an orthopaedic clinic that, even at the expense of appearing tedious, I shall call your attention to a few of the commonest types, and emphasize some of the measures that may be used in their prevention.

The surgeon when confronted with a fracture must make an exact diagnosis and base his treatment on that diagnosis. Fortunately, we have in the roentgenogram the means at hand definitely to show the break and the relation of the fragments. Unless for very good reasons, for example, the inaccessibility to a roentgenographic apparatus, or the poor condition of the patient, a roentgenograph should be taken of every fracture or suspected fracture. The picture intelligently interpreted settles the pathology at once and affords the sound basis so necessary for rational treatment.

### THE SHOULDER JOINT

Following a fracture in the region of the shoulder joint, the usual disability is lack of abduction and outward rotation. This may ensue even when the reduction of the fracture is perfect, since the inflammatory exudates cause periarticular adhesions. If the disability is due solely to periarticular adhesions, it is readily relieved by breaking them up under an anesthetic, followed by massage and the active

\* President's address before the Southern Minnesota Medical Association, Mankato, January, 1919.

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exercise of the joint; if it is due to an actual bony deformity, it is clearly the fault of the setting.

In a fracture of the anatomic neck, if reduction cannot be perfect without an open operation, a slight amount of displacement may be permitted and the operation avoided as there is almost always good impaction, and union is sure to occur. The danger lies in the limitation of motion that may follow. If the patient can stand the confinement, he may be put to bed with the arm abducted to a right angle, the position being maintained by a Buck's extension with a light weight attached. At the end of two weeks union will be sufficiently firm so that the arm may be gradually dropped to the side. The abducted position to a right angle should be resumed by passive motion at least three times daily.

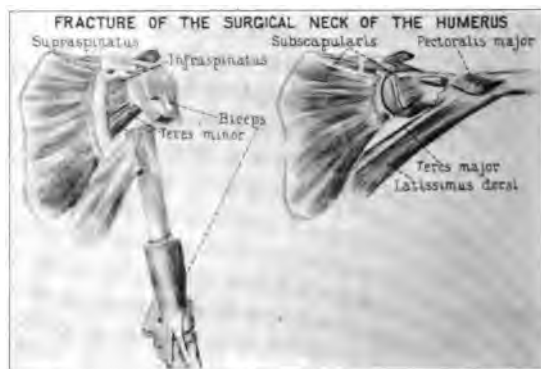


FIG. 436.—Fracture of the surgical neck of the humerus.

If the fracture is situated at the surgical neck, the tendency is for the pectoralis major, the teres major, and the latissimus dorsi to draw the lower fragment inward. The supraspinatus, infraspinatus, and teres minor, as opposed to the subscapularis, tend to abduct and outwardly rotate the head and upper fragment (Fig. 436). The tendency of the biceps and triceps is to pull the lower fragment up and past the lower end of the upper fragment. If malunion occurs in this position it is readily seen that abduction and outward rotation will be limited. If satisfactory reduction and firm impaction by strong extension (best conducted in abduction to a right angle or in the extreme position with the arm parallel with the head) can be accomplished and the ends impacted, the arm may gently be brought to the side and strapped there after an auxiliary pad is placed in position.

If the arm is held in abduction at a right angle after reduction and impaction, the pull of the pectoralis major, latissimus dorsi, and teres major is in the long axis of the bone and the muscles do not tend to slip the fragments past one another (Fig. 436). The maintenance of the arm in abduction by a Buck's extension for two weeks, followed by the gradual dropping of the arm with tri-daily resumption of right angle abduction, is a form of treatment which insures a good result. In the case of a bad intra-articular fracture in which ankylosis or marked limitation of motion is unavoidable, the ankylosis should be allowed to occur with the arm in abduction at a right angle. The movement of the scapula on the thorax, when the head of the humerus is ankylosed at a right angle to the neck of the scapula, permits a very satisfactory range of motion for the arm.

#### THE ELBOW JOINT

Fractures near the elbow joint are noteworthy for the bad results that may ensue. The common deformity is lack of ability to flex the elbow sufficiently to permit of ability to dress, for example putting

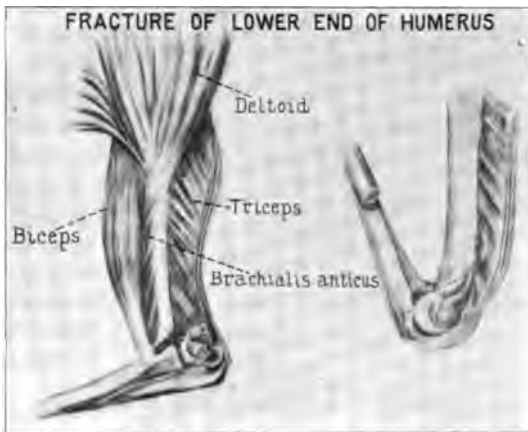


FIG. 437.—Fracture of the lower end of the humerus.

on a collar or, in the case of a woman, dressing the hair. If the head of the radius is involved in the fracture, there may also be lack of pronation and supination. Sir Robert Jones lays down the following golden rule for the treatment of fractures of the elbow: "They should all be treated with the elbow fully flexed and the forearm supinated with the single exception of fracture of the olecranon, which requires

full extension." The loss of flexion so dreaded may be due either to imperfect reduction or excessive callus formation. In a supracondylar fracture the lower fragment, as a rule, is displaced backward, the upper fragment is displaced forward in front of the lower and is a mechanical obstruction to full flexion unless the reduction of the fracture is complete (Fig. 487). Such a fracture is best reduced by partial flexion of the elbow to a right angle or more, and the exertion of firm, strong downward traction on this and manipulation of the lower fragment onto the upper. The latter part of such a reduction is greatly aided by complete flexion of the elbow with the forearm in supination. The strong tendon of the triceps muscle posteriorly and the coronoid process of the ulna with the attached muscles in front, steady the fragments in position. For the subsequent treatment I quote again from Sir Robert Jones: "After three or four days, when absorption of the immediate exudates is well advanced and repair has begun, and when in particular the muscles have come to rest, the elbow need not be so acutely flexed, but the forearm should be slung by the wrist close under the chin. Between the second and third weeks, when bony union is fairly secure, the wrist may be dropped two or three inches, and the patient may practice active movements daily, producing full flexion and then allowing the arm to fall down to the limit allowed by the sling. If the movement can be satisfactorily performed, the sling can be lengthened every two or three days until a right angle is reached when it can be discarded altogether." The right angled splint so often seen need only be mentioned to be condemned. No splint is necessary in the treatment of fractures in the region of the elbow with the exception of those of the olecranon process of the ulna. With the elbow flexed and adhesive plaster placed around the arm and forearm, the position is very nicely maintained. If the fracture involves the condyles, thus being intra-articular, there is often a spreading, as it were, of the elbow. Manipulation and forcing of the joint into acute flexion will usually control the fragments as well as they can be controlled. If a piece of one of the fragments lodges in front of the joint and prevents flexion, an incision must be made and the obstructing piece removed. It is true that full motion will not be obtained by any method in this intra-articular type of fracture but satisfactory flexion will be secured. When the neck or head of the radius is fractured it may be necessary to remove the head, but not infrequently the fully flexed position with the hand in full supination will secure a very satisfactory result.

## THE WRIST JOINT

It is not uncommon to see deformity and disability following a Colles' fracture. The dinner fork deformity causes pain, soreness and inability to grasp objects. This is almost always due to inefficient reduction. There are undoubtedly a certain number of Colles' fractures in which the force causing the impaction at the time of the accident is so great that a good deal of the cancellous bone is destroyed and the normal contour of the wrist cannot be restored. In such cases the aim must be to break up this impaction to such a degree that the normal line of the continuity may be restored as nearly as possible and the muscles permitted to pull in their normal axis. Even if there is considerable radial deflection because of loss of substance in the radius, function will be remarkably good if the fragments are in the same anteroposterior plane. In my experience the textbook plan of reduction by grasping the patient's hand and pulling is not in itself sufficient. The patient is seated in a chair and an assistant grasps firmly the patient's forearm which is held midway between pronation and supination. This leaves both hands of the surgeon free; he then grips the hand of the patient in the usual way and pulls firmly; as his other hand is free, he is able, by pressure with the thumb and forefinger on the fragments, to force them into line and to mould them in position. If the patient is seen immediately after the accident and before much swelling has occurred, the sense of touch conveys the knowledge that reduction is complete. The patient usually volunteers that "it feels much better." If such relief is not experienced one should be guarded in any statement as to complete reduction. In certain cases I have used the following method of Sir Robert Jones with happy results. "To reduce a left Colles' fracture the surgeon takes the patient's arm in his left hand, with his own scaphoid tubercle against the projecting lower end of the shaft; he then places his right hand on the dorsum of the patient's wrist with his own scaphoid on the projecting lower fragment. A firm grip with a slight traction and twist of the wrist completely reduces the deformity. It requires knack rather than strength." If reduction is complete almost any splint will hold the fragments. Early use of the fingers should be encouraged but the wrist should not be actively used for about four weeks.

## ISCHEMIC PARALYSIS

A consideration of deformities following fractures would be incomplete without mentioning ischemic paralysis, a fearful sequela too often caused by neglect. I have in a few instances seen ischemic paralysis in cases in which no splints had been applied. It is possible that a hemorrhage occurred in these few instances and, held in by the strong fascia of the forearm, caused sufficient pressure to devitalize the muscles and nerves. The vast majority of the records state that the fracture was reduced and tight splints applied, and in spite of the agony of the patient and entreaties of relatives and friends for their removal, that they were left on and when finally removed irreparable damage had been done. If the pain following the reduction and splinting of a fracture is extreme, the splints should be loosened at once. Ischemic paralysis is occasionally seen in the lower extremity.

## NON-UNION

Just when delayed union becomes non-union cannot definitely be stated. Some authorities say that we should always speak of the condition as delayed union, but when it persists for from seven to eight, ten or fourteen years, it would almost seem that the term delayed union applied to such cases is a little farcical. Various conditions such as syphilis and poor blood supply are mentioned as being responsible for its presence. Improper reduction and early rough handling to determine whether or not union is occurring are often responsible, but the chief cause for non-union is probably the interposition of muscle between the bone ends. In a considerable number of ununited fractures I have seen but one in which syphilis might have been the cause of non-union.

## THE HIP JOINT

The large number of ununited fractures of the hip (Fig. 438) that are seen is chiefly owing to the fact that the fracture was not recognized and that no treatment was instituted because the condition was erroneously diagnosed sprain. In any injury to the hip, particularly in the aged, a roentgenogram should be made at once unless the symptoms are so classical that the diagnosis of a fracture of the neck can be made and the proper treatment carried out. Even then, it is much better for all concerned to insist on a roentgenogram. From the observation of a

considerable number of these cases I am convinced that it is almost always better to break down the impaction and to reduce the fracture just as we do a Colles' fracture. The term impacted fracture, the degree of impaction being so difficult to determine in the roentgenogram, gives, I am sure, a feeling of false security. Undoubtedly many



FIG. 438.—Ununited fracture of the hip showing total absorption of the neck of the femur.

of these impactions break down later and non-union results. With reduction accomplished, some means should be taken whereby it is maintained. Whitman's abduction method and the Ruth-Maxwell traction methods are both efficacious. Under proper conditions open operation is permissible and a beef-bone screw placed through the trochanter and neck and into the head insures proper position.

#### THE KNEE JOINT

A supracondylar fracture or one in the lower one-fifth of the femur so alters the line of weight-bearing in the knee as to cause serious disability (Fig. 439); this is occasioned by the posterior displacement of the lower fragment. While much is written concerning the efficacy of certain splints in the treatment of this type of fracture, if the separation of the fragments has been so extreme as to allow muscle to be interposed between the fragments, conservative measures are almost

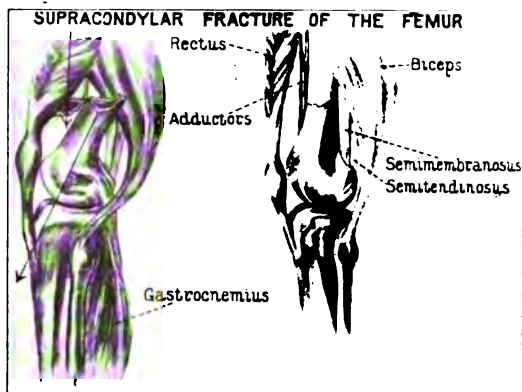


FIG. 439.—Supracondylar fracture of the femur.

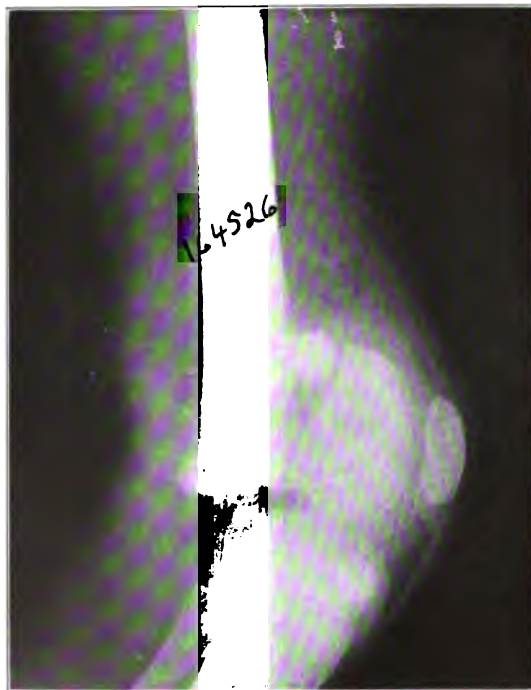


FIG. 440.—Epiphyseal separation of the lower end of the femur with the epiphysis looking directly forward.

invariably fruitless. If proper surroundings and sufficient surgical skill can be obtained, such a fracture should be opened and the fragments coapted and held in place by whatever means is, in the judgment of the surgeon, correct, be it a metal plate, nails, or bone graft. It is remarkable to what extent displacement of the fragments may occur with, comparatively speaking, slight external evidence, and unless one is acquainted with such a fracture, the roentgenogram will be startling. This is especially true of separation of the epiphysis in children (Fig. 440), in which the condyles of the femur are found on the anterior surface of the lower end of the shaft of the femur, with the articular surface looking directly forward. In the latter type it is generally necessary to expose the fragments by splitting the patella longitudinally, opening wide the knee capsule, splitting the posterior layer of the synovial sac at will, and by manipulation and prying to force the epiphysis back into place. The results are usually excellent with full function of the knee.

#### THE ANKLE JOINT

Pott's fracture consists of a fracture of the fibula 2 or 3 inches above the tip of the external malleolus, the strong tibio-fibula ligament

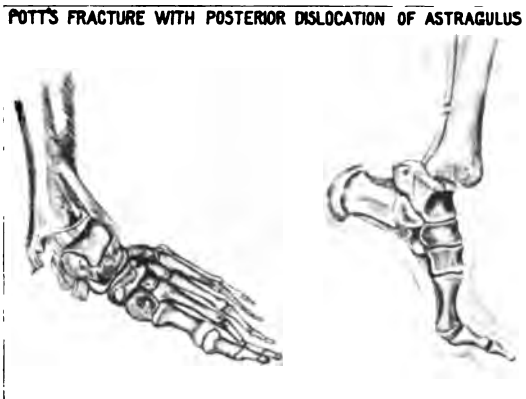


FIG. 441.—Pott's fracture with posterior dislocation of astragalus.

prevents fracturing any lower, and a tearing of the internal lateral ligament with occasionally part of the tip of the internal malleolus (Fig. 441). There is not infrequently a posterior displacement of the astragalus. There may be a break of the anterior lip of the lower articular surface of the tibia which is a troublesome complication. If



the force has been quite severe the astragalus may be driven upward so that the external superior articular border acts as a wedge and crushes and forces up the external margin of the tibial articular surface, making, as it were, a groove for the astragalus to fit into and rendering reduction more difficult, with a resulting tendency for the deformity to



FIG. 442.—Brace to be used following Pott's fracture showing outside iron, inside T strap and raised inside sole.

recur. The common deformity seen after this fracture is marked eversion of the foot with the weight-bearing line falling to the inner side. The disability is great. Reduction should be complete and nothing short of this should be accepted. The foot should be held in slight inversion; the ankle should be dorsiflexed to at least a right angle, and care taken that the posterior displacement of the astragalus,

sometimes present, is corrected. Weight-bearing, if too early, may have serious results and should not be permitted under six weeks, for a good position may be lost through the giving way of a soft callus. The inner side of the sole of the shoe and heel should always be raised so that the foot will be placed in slight inversion, and held so for six weeks. For heavy persons it is often wise to provide in addition an outside iron and inside T strap (Fig. 442).

#### SUMMARY

Following a fracture in the region of the shoulder joint, the common disability is lack of abduction and external rotation; in the region of the elbow, lack of flexion, and in the region of the wrist there is the well known dinner-fork deformity with inability to close the fingers. A fracture in the hip is prone not to unite unless adequate fixation is provided after the reduction. A supracondylar fracture of the lower end of the femur or an epiphyseal separation interferes with the proper transmission of weight through the joint surfaces and limits flexion and extension. Pott's fracture is the common fracture of the ankle and not infrequently causes disability by the valgus produced by poor alignment for weight bearing.

If the type of deformity that is apt to follow the particular fracture being dealt with is kept in mind, and if it is recognized that the deformity is potential, better results will undoubtedly be obtained by so vigorously directing the treatment as to guard against poor alignment of the fracture.



## **NERVES**



## STUDY X: THE ETIOLOGY AND TREATMENT OF ACUTE POLIOMYELITIS\*

E. C. ROSENOW

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The studies I have made on the elective localization of bacteria indicated that the methods used in studying the localizing power of the bacteria isolated by a number of observers in poliomyelitis, were not adequate to rule out their possible etiologic relationship. The results in herpes zoster were especially suggestive. Green-producing streptococci, it will be recalled, were isolated from tonsils, pyorrheal pockets, sputum, and from the spinal fluid at the height of attacks of severe herpes zoster which, when injected intravenously into animals produced herpes associated with lesions and localization of the streptococci in the posterior root ganglia. The infiltration in the posterior root ganglia in herpes zoster is similar to the infiltration of these ganglia in spontaneous experimental poliomyelitis.

Head and Campbell regard herpes zoster as an acute infectious disease which confers immunity, and suggest that it be designated as acute posterior poliomyelitis in contradistinction to acute anterior poliomyelitis. The possibility of a close relationship of the microbial cause in these diseases is further suggested by the observation of Romer who found that the serum of patients with herpes zoster neutralized the virus of poliomyelitis. Owing to these results a re-study of the bacteriology and the localizing power of bacteria of ordinary size obtainable from the throats and tonsils and from the nervous system in poliomyelitis was undertaken. That the pleomorphic streptococcus found in such large numbers in throat and tonsil and in smaller numbers in the nervous system bears etiologic relationship to poliomyelitis is indicated by facts determined since my studies were begun two years ago as follows:

It is constantly present in the diseased tissues, from which it may be cultivated even many months after glycerolation. On injections

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of cultures into young rabbits and guinea pigs it localizes specifically in the nervous system and produces flaccid paralysis and changes in brain and cord which resemble those in poliomyelitis in man. From the brain and cord of these animals the organism may be isolated and the disease again produced. The organism has been rendered filtrable. By means of the same methods the identical organism has been isolated constantly from the brain and cord of monkeys paralyzed with fresh, glycerolated and filtered virus. The serums of persons and of monkeys having recovered from poliomyelitis agglutinate specifically the more sensitive strains both from human and monkey poliomyelitis. Injections of the recently isolated aerobic cultures into monkeys renders them refractory to virus. The aerobic form of the organism from human and monkey poliomyelitis produces antibodies in the serum of horses, in a large amount common to both, cross-agglutinating these strains specifically in high dilution. The serum of a horse immunized with freshly isolated strains from monkeys protected monkeys relatively against intracerebral inoculation of virus and had pronounced curative effects in the treatment of human poliomyelitis. Early intravenous injections were followed by almost immediate cessation of symptoms in a large series of cases.

The results of Flexner and Noguchi, so far as the cultivation of a small filtrable organism and its demonstration in the tissues in poliomyelitis are concerned, have been corroborated, but the results of our experiments indicate that this is the anaerobic and, according to Amoss' results, a non-antigenic form of the organism which, under aerobic cultivation, clearly belongs to the streptococcus group of microorganisms. Both forms have been constantly demonstrated side by side in the tissues of poliomyelitis. Flaccid paralysis coming on soon after injection has been produced in monkeys with characteristic, although not typical, changes in the cord with aerobic cultures, but the classic picture as obtained with virus in this species has not been secured.

It may be suggested, however, on the basis of results already obtained, that this is due to the development of antibodies, since the organism in the aerobic form has marked antigenic powers.

The serum used in the treatment of cases heretofore was prepared by injecting freshly isolated strains from the brain and cord of monkeys that had succumbed to experimental poliomyelitis. During the past year, owing to the inability to procure monkeys on account of the war,

the method of preparing the serum had to be modified and the strains for injection were isolated from glycerolated poliomyelitic material. Opportunity further to study this disease and to test the efficacy of the newly developed serum was afforded in the recent epidemic of poliomyelitis in Dubuque, Iowa. The results of animal experiments obtained in two previous epidemics were verified and extended. Conditions for studying the effects of the serum were ideal. The epidemic had begun two weeks previously. The number of cases were increasing and continued to increase for two weeks after the serum treatment was begun, and then gradually subsided. The symptoms and paralysis were marked. The mortality rate was high; 8 of the 17 patients who were reported as having the disease died and most of the others showed marked paralysis. Three patients died during the night immediately prior to the institution of the serum treatment. In 4 of the 11 patients treated with the serum on the first two days the prognosis was most unfavorable. The serum was administered to all patients irrespective of the stage of the disease. The diagnosis was established by spinal puncture. The mortality rate dropped from 47 per cent before to 4 per cent after the serum treatment had been instituted. Altogether 54 patients were treated. These may be considered in three groups: (1) those without paralysis; (2) those with slight paralysis, and (3) those with advanced paralysis at the time of the serum treatment.

There were 20 patients in the first group. All recovered without developing paralysis. There were 15 patients in the second group. The paralysis was arrested in all but 3 in whom slight extension occurred. All have recovered completely or are showing rapid improvement. There were 19 patients in the third group; 2 died. One was a poorly nourished weak baby two weeks old, who showed no distinct paralysis but had refused nourishment during a period of seven days and gradually grew weaker and died seemingly of malnutrition. This is included as a case of poliomyelitis almost wholly on the spinal fluid findings. There were a positive globulin test and 40 cells to the cubic centimeter. One subcutaneous injection of 6 c.c., of serum was given with no apparent effect. The other death was in the case of a girl of 18, who had been severely ill for four days. A rapidly progressing paralysis of the ascending type began thirty-six hours previously. At the time of the first injection there was practically complete paralysis of both lower extremities, paralysis of the muscles



of the back, of the bladder and rectum, of the left arm, a marked weakness of the muscles of the right arm, neck and muscles of deglutition, and marked shortness of breath with cyanosis owing to involvement of the muscles of respiration. The temperature was lowered and the paralysis was arrested for forty-eight hours. Eighteen hours after the third injection of serum respiratory embarrassment recurred and the patient died twelve hours later.

In the remaining 17 patients the paralysis was arrested in those in which it was progressing. A distinct improvement in muscle function occurred soon after injection in those in whom the paralysis was stationary. Postparalytic pains, if still present, were relieved, as long as ten days after onset in those in whom the spinal fluid still showed evidence of activity of the process. It is too soon to give the details of the final outcome in these cases. The preliminary results show, however, that the newly developed serum has distinct curative power in poliomyelitis. The results moreover indicate that the loss of muscle-function in the early part of the attack is due, in large part, to inhibition of physiologic function, and not to death of the ganglion cells in the anterior horns. The amount of good which followed the injection of serum was quite in proportion to the time of the injection following the onset of symptoms. Hence, in order to obtain the best results, the injection of serum should be given at the earliest possible moment, preferably before paralysis has begun, and before infiltration and edema in the anterior horns has become marked.

Dead ganglion cells can not regenerate and not too much should be expected from the injection of serum when their death has occurred. This disease has a quite characteristic syndrome which should lead to its tentative diagnosis and to immediate spinal puncture. However, there are some cases in which the premonitory symptoms are so slight as to escape notice; the paralysis sometimes is the first noticeable symptom. Hence the final solution of the problem of poliomyelitis must come from prevention, and from prophylactic immunization with a suitable antigen. Experiments along this line are now in progress.

Abortive attacks were numerous in this epidemic. Many children had symptoms resembling those of poliomyelitis which were too vague to lead to a positive diagnosis. A careful study of the state of health of others in the family in which typical cases occurred, and of the general health of the community at the time of the epidemic,

the details of which will appear subsequently, brings with it the conviction that a large proportion of the population harbored this infection and that only one case out of the usual number (1 in 600 to 1 in 1,000 inhabitants) developed the typical syndrome recognized as poliomyelitis. From the studies I have made the infection appears to be due to a form of streptococcus (using this term in the broad sense) having peculiar localizing powers and specific immunologic reactions. In this connection it is of interest to note that the incidence of poliomyelitis in families and the community at large during epidemics in summer, is about that of rheumatic fever or pneumonia during the colder seasons when the more virulent streptococcal respiratory and tonsillar infections are prone to occur in epidemic form.

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## A CLINICAL STUDY OF NERVE ANASTOMOSIS\*

A. W. ADSON

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THIS paper represents the results obtained in 41 cases of nerve anastomosis performed in the Mayo Clinic up to Jan. 1, 1917. Cases in which postoperative records are shorter than sixteen months are not included in the report.

In 1852 two theories of nerve regeneration were advanced; one, that the axons grow out from the central end, that complete degeneration takes place from the severance of the nerve proximal to the node of Ranvier, and distally through the entire peripheral nerve; and the other, that the axons do not degenerate in the peripheral stump after they have been separated, and that the fusion with the central axon and the development of the new myelin sheath about it is necessary to enable an axon to functionate.

The modern work on the regeneration of nerves may be said to have been begun by von Büngner in 1891, followed by Howell and Huber in 1892, by Ströbe in 1893, and by Huber in 1895. von Büngner called attention to the nucleated protoplasmic bands which have been so conspicuous in the histogenesis of regenerated nerve fibers. He emphasized the fact that the nuclei of the neurolemma increase in number and that the protoplasm accumulates about them. Howell and Huber observed the presence of protoplasmic bands (*Bandfasern*), but regarded them as embryonic nerve fibers capable of receiving and transmitting impulses. Ströbe was able to demonstrate the outgrowth of axons from the central end but believed that the myelin sheath was formed as a continuation of the old sheath. Huber, working with Ströbe's technic, was able to show that the axons grew from the central stump and in some cases entered the substance of the protoplasmic bands in the distal segment. Ranson, in 1912, presented his work on the degeneration and regeneration of nerve fibers, in which he verified the investigations made by Waller, in 1852,

\*Reprinted from *Ann. Surg.*, 1919, lxx, 159-168.

and gave a clear description of the processes of degeneration and regeneration, as well as a thorough review of the literature. Kirk and Lewis, in 1915, and 1916, also presented a very complete histologic study of nerve regeneration.

Nerve anastomosis has been accomplished by the use of methods as follows: Létiévant made flaps from the central or the peripheral stump of the divided nerve, or from both the central and peripheral stumps. If it was impossible to bring about an immediate approximation of the nerve ends, various materials were used to bridge the gap. Assaky recommended a bridge of catgut between the severed ends, Vanlair used decalcified bone tubes, Payr magnesium tubes, Forssman celluloid tubes, Lotheissen gelatin tubes, Foramitti the hardened arteries of the calf, Denk, Döpfner, Kredel, and Kirk and Lewis fascia lata tubulization, Corbett and Beckman vein tubulization, Sherren Cargile membranes, Auerbach galalith, and Assaky and Hubner nerve transplants. Feiss used the fusion method of overlapping the ends and ligating them with silk or chromic catgut.

All of the various methods of nerve anastomosis have been discarded except: (1) the flap method, (2) the fusion method, (3) fascial tubulization, (4) vein tubulization, (5) Cargile membrane tubulization, (6) nerve transplantation, and (7) end-to-end anastomosis.

The nerve flap method, described by Létiévant, has been used extensively by operators in general surgery. Their patients improve, but the degree of improvement is not accurately stated in their reports.

The fusion method was advocated and tried out experimentally by Feiss, who believed that regeneration depended more on the regenerating scar than on the approximation of the nerve ends.

Fascial tubulization was brought to our attention recently by Kirk and Lewis, who presented a study on experimental tubulizations as well as reports of clinical tubulizations. However, the fascia lata had been used by former workers, for example, Denk, Döpfner, and Kredel.

Vein tubulization was described by Corbett, who employed very much the same technic that Kirk and Lewis used in their fascial tubulization, namely, removing a large portion of vein, dividing it longitudinally and placing it around the severed ends of the nerve as a piece of fascia. Beckman used the resected vein as a closed tube, slipping the cuff of vein over one of the nerve ends prior to anastomosis and then bringing the vein back over the intervening gap, and surrounding the cylinder of silk.

Sherren recommended the use of Cargile membranes, the fixed peritoneal membranes of the ox, for the purpose of tubulization.

Nerve transplants were suggested and tried experimentally by Philippeaux and Vulpian. They were used by Assaky in clinical cases and by Huber in a series of experimental cases. Huber reports twenty-six experiments made on the foreleg nerves of dogs. Ten were observed for a period of time long enough to permit regeneration of the peripheral stump, five of which presented complete and four nearly complete return of function.

It is rather difficult to classify the results of the various operations reported in the literature on the subject. Speiser, in 1902, collected 208 cases of nerve suture; these combined with 129 cases collected by Schmidt make 337. Two hundred thirty-four patients (66.5 per cent) obtained good results, 53 (15.5 per cent) obtained partial relief, while 60 (18 per cent) were not improved by the operation.

Sherren reported 4 (50 per cent) successful cases in 8, by the autotransplant and homotransplant methods, and Huber reported 37 per cent of successes in 22 cases of heterotransplants.

Oberndörffer reported 167 cases of nerve sutures, in 96 of which operations were done the day after the injury. Good results were obtained in 38 per cent, fair results in 35 per cent, and failures in 16 per cent; the results in 11 per cent were unknown. In cases in which operations were done from two to seven days after the injury, good results were obtained in 35 per cent and fair results in 52 per cent; the results were unknown in 15 per cent. In the operations done from eight to fourteen days after the injury good results were obtained in 57 per cent and fair results in 43 per cent. In operations from three to four weeks after the injury good results were obtained in 56 per cent, fair results in 32 per cent, and failures in 12 per cent. In operations from five to eight weeks after the injury good results were obtained in 44 per cent, fair results in 25 per cent, and no improvement in 31 per cent. The statistics with regard to nerve suture, compiled by different men, show that good results were obtained in 70 per cent of the cases.

#### HISTOLOGY

A brief review of the histology of peripheral nerves will call attention to the fact that the fibers of medullated nerves arise from the anterior horn cells and join the fibers from the dorsal root which con-

tains both medullated and non-medullated fibers (Ranson). The non-medullated nerve fibers have their origin in small ganglion cells in the dorsal ganglion, and have axons surrounded by a neurolemma without myelin. The medullated nerve fibers have an axilemma next to the axis cylinder; this is surrounded by the myelin sheath, which in turn is surrounded by a neurolemma (Schwann's sheath). The myelin is divided into segments by the nodes of Ranvier. Elongated cells which are of the utmost importance during the process of regeneration are associated with Schwann's sheath.

*Degeneration and regeneration.*—Immediately following the division of the nerve, abortive regenerative processes take place; that is, the axis cylinder in both the proximal and distal stumps (more pronounced in the proximal end) undergoes fibrillar disintegration with an outgrowth of fibrillæ within the neurolemma. This process extends back for a distance of about 3 mm. and begins within the first thirty-six to seventy-two hours following the severance of the nerve. At the same time the nuclei associated with the Schwann's sheath start a process of hyperplasia which begins with enlargement of the nucleus and a granular deposit in the cytoplasm. The wallerian degeneration begins about the third day and is quite complete on the twelfth day, except for the resistant axons and the myelin granules that may be seen for several weeks. This process consists of a granular disintegration of the axon in the distal end and of the axon in the proximal end up to the first node of Ranvier. The myelin begins to disintegrate and forms droplets of fat within the neurolemma, thus giving a positive black stain with Marchi's method, whereas the normal myelin gives a yellow stain.

The regenerative process is continuous with the degenerative process; first, the nuclei of Schwann's sheath multiply very rapidly and fill the empty lumen of the neurolemmal sheath in the distal end as well as the sheaths from the site of severance to the first node of Ranvier; then, if the intervening gap between the severed ends is not too long, or if it is protected by some form of tube, these cells will send out protoplasmic bands of gelatinous appearance, which fill the intervening gap. Simultaneously the axon sends out numerous neurofibrillæ, numbering from five to fifteen, which grow downward through the mass of protoplasmic bands, and, if the gap has been bridged by these bands, they follow the bridge and enter the distal nerve segment. It is not uncommon to find two or three axons fol-

lowing a single protoplasmic band. Many of the neuraxons, however, will fail to enter the distal nerve segment and will produce an oval enlargement at the site of anastomosis, known as a neuroma.

The protoplasmic bands and cells arising from the neurolemmal sheath not only assist in keeping the lumen of the distal segment open and bridge the intervening gap between the nerve ends, but also apparently they arrange themselves and act as a reticulum, forming the mesh work in which the myelin is deposited, enabling the nerve to complete its process of regeneration. The following outline is quoted from Ranson:

*"Early changes in the distal stump.*—1. Degeneration of the medullated fibers and formation of nucleated protoplasmic bands. 2. Degeneration of the non-medullated fibers and the formation of nucleated protoplasmic bands. 3. Abortive autogenous regeneration in the distal stump.

*"Early changes in the proximal stump.*—1. Changes in the non-medullated fibers; early abortive regeneration; cellulipetal degeneration; formation of new axons. 2. Changes in the medullated fibers; formation of zone reaction; fibrillar dissociation; early branching of the axons in the immediate neighborhood of the lesion; formation of lateral branches at some distance above the lesion; formation of fiber bundles and skeins.

*"Mechanism of the regeneration of nerve fibers.*—1. Proliferation of axons in the central stump. 2. Penetration of the new axons through the scar. 3. Utilization of the protoplasmic bands as pathways for the new axons in the distal stump."

#### CLINICAL FINDINGS

All the patients had preoperative neurologic examinations, and many returned for subsequent examinations. We secured data of the patients who were unable to return by correspondence and by the coöperation of local physicians.

Nine facial anastomoses were made (five females and four males). The average age of the patients was twenty-four years. Eight (89 per cent) of the 9 patients have been examined at intervals following operation, or they have reported by letter. The average duration of the injury before the anastomosis was made was twenty-six months. The 3 patients who were operated on within the first year following the injury showed improvement of from 60 to 85 per cent in return

of function. The patients operated on at varying periods of time up to five years showed an improvement up to 50 per cent of function. One patient, with a fifteen-year history, failed to reply to the "follow-up" letter. The injury of the nerve in 2 cases was due to a mastoid operation and in 7 cases to a lacerated wound in the region of the seventh nerve. In 8 cases the anastomosis was to the spinal accessory, in one case to the hypoglossal. In 8 cases end-to-end anastomoses were made, three of which were covered with fascia, four with vein, and one was left uncovered. In one case the anastomosis was by the Feiss method; the nerve ends were overlapped and ligated with silk.

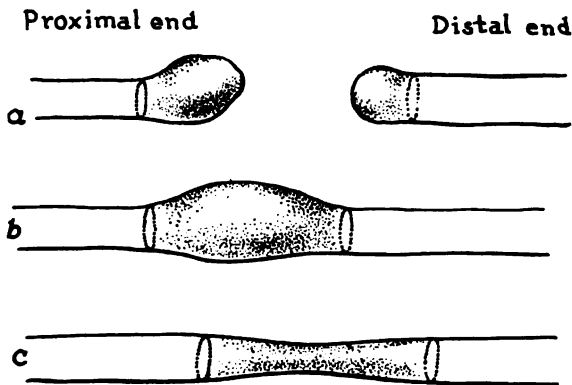


FIG. 443.—Clinical findings in peripheral nerve injuries; (a) severed nerve with neuromas and lines indicating the level of resection prior to anastomosis; (b) neuroma due to trauma without severance of the nerve; (c) constriction of nerve due to scar tissue or callus.

The average time before improvement was noticed, following the anastomosis, was seven and nine-tenths months; the average time for maximum improvement to be reached was eighteen and one-half months. The average amount of motor return estimated by quantitative examination of the power and control of the facial muscles was 71 per cent of the normal function.

In summing up the results, it is found that in 89 per cent of the patients heard from, all of whom had improved, the average amount of improvement was 71 per cent, and in this group there were no failures nor indeterminate results, no infections, and no deaths.

Seven ulnar anastomoses (in one female and six males) were made. The average age of these patients was twenty and four-tenths years. Five (71 per cent) were heard from or were studied following operation.



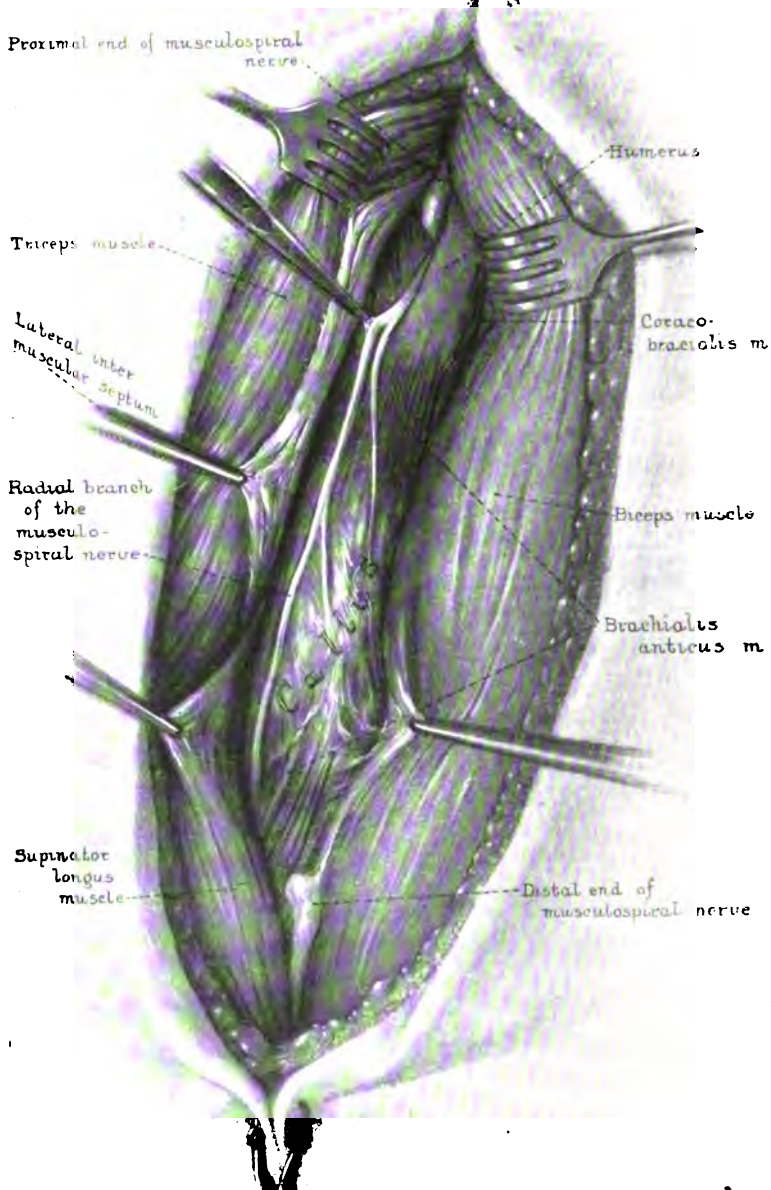


FIG. 444.—Anatomic relations of the proximal and distal neuromas of the musculospiral nerve, following complete severance at the time of fracture of the humerus.

The average duration of the injury before the anastomosis was six months, the shortest six weeks, and the longest twelve months. Two of the injuries were associated with fractures of the elbow and two with lacerated wounds of the forearm. Six of the anastomoses were made with silk sutures and one with chromic catgut. Three were



FIG. 445.—Anastomosis of the musculospiral nerve with silk. Stitches placed in the epineurium.

covered with fascia. In 5 cases the apposition was direct, without a gap; in 2 the gap, which was an inch long, was covered with a tube of fascia lata. The average time before improvement was noticed in these cases was ten months; the average time before maximum improvement was noted was sixteen and two-tenths months. The amount of maximum improvement in the patients who reported was

63 per cent of the sensory, motor, and trophic functions. There were no failures nor indeterminate results, no infections, and no deaths.

One radial anastomosis was made. The patient, a man aged twenty-four years, was operated on two months after the injury. The anastomosis was done with silk. Unfortunately, we have not been able to obtain a report from this patient since he left the clinic.

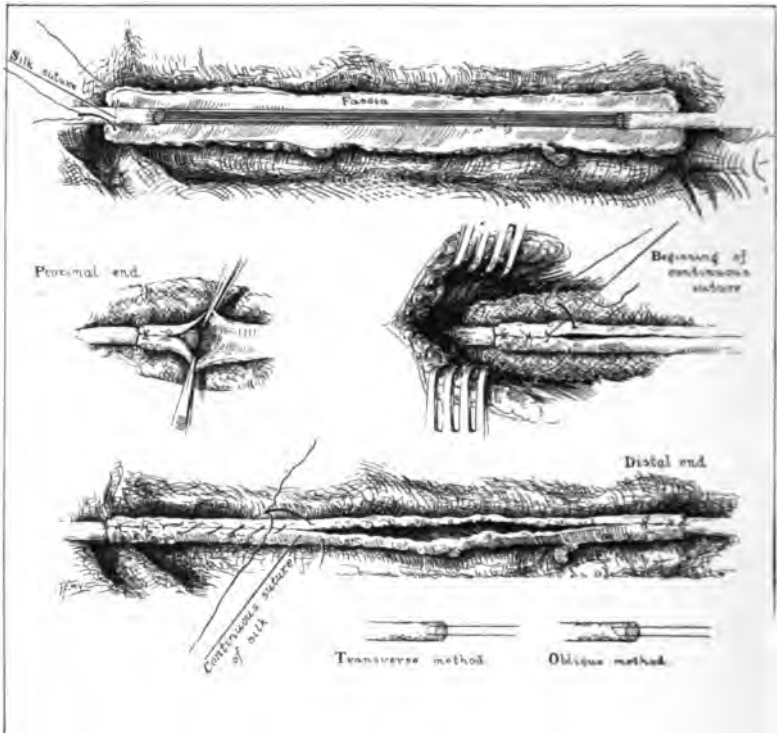


FIG. 446.—Method of anastomosis with silk and fascia. Various steps shown in the covering of the cylinder of silk with fascia.

Seven median nerves were repaired. All the patients were males; their average age was twenty-three years. Six (85.7 per cent) of these patients have been heard from, or have been studied following operation. The average duration of the injury before operation was eighteen months, the shortest six weeks, the longest four years. Five patients were operated on within the first year, two gave a four-year history; all the injuries were due to lacerated wounds. In 3 cases the anastomoses were made with silk, in 3 with chromic catgut, and

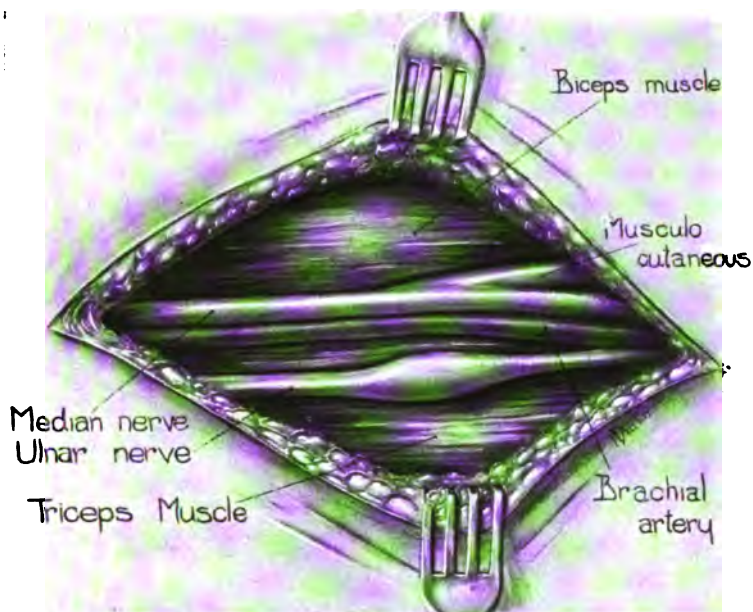


FIG. 447 (202189).—Exposure of the ulnar nerve in the right upper brachial region with a large neuroma due to trauma, without severance of the nerve.

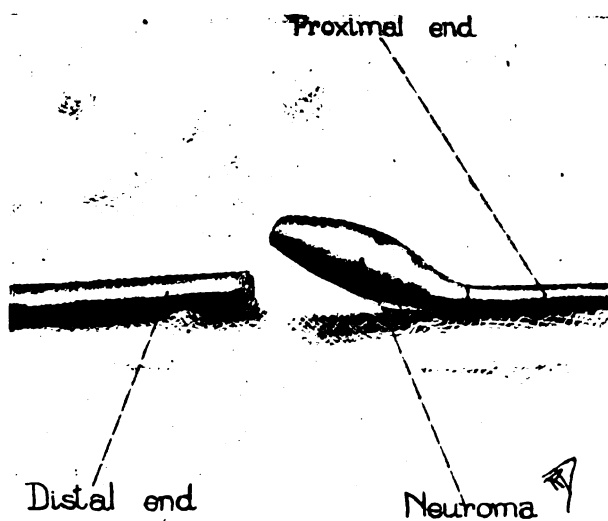


FIG. 448 (202189).—Resection of neuroma previous to anastomosis.

in one a plastic operation was done. In 5 fascia covering was used, in 2 the nerve was left uncovered. Direct apposition was obtained in 5 cases; in 2 a gap of one inch separated the severed ends. The average time before improvement was noticed was ten and nine-tenths months, the average time before maximum improvement was reached

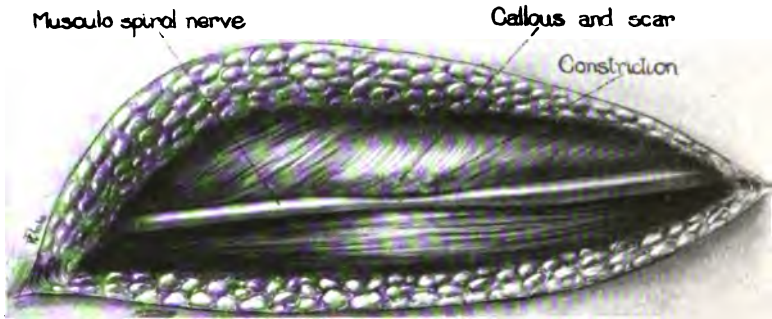


FIG. 449.—Exposure of the left musculospiral nerve, constricted by an exuberant callus and scar, without complete destruction.

was twenty-one months, with 72 per cent return of the sensory, motor, and trophic functions. There was, therefore, in the patients heard from, improvement in 71 per cent, one failure, no indeterminate results, no infections, and no deaths.

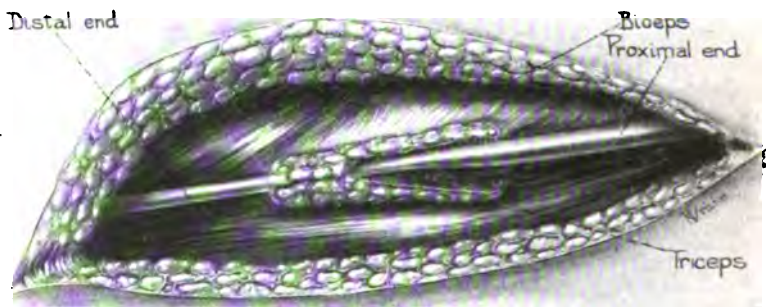


FIG. 450.—Covering the constricted musculospiral nerve with a fascial flap to avoid further constriction.

Ten musculospiral anastomoses were done; all the patients were males, whose average age was thirty-six years. Nine (90 per cent) were heard from after operation. The average duration of injury was twenty-eight months, the shortest two and one-half months, the longest twelve years. Nine of these injuries were associated with



fractures of the humerus; one was due to a lacerated wound. Seven of the anastomoses were end-to-end, with silk and chromic catgut sutures. In two the operations were plastic; a segment of the proximal end was turned down. In one case the nerve was freed from adhesions. In 7 cases the anastomoses were covered with fascial tubes; in 4 of these a gap of from one-half to one and one-half inches separated the ends of the nerves. The average time before improvement was noticed was twelve months; the average time before maximum improvement was noted was twenty-seven months. The amount of

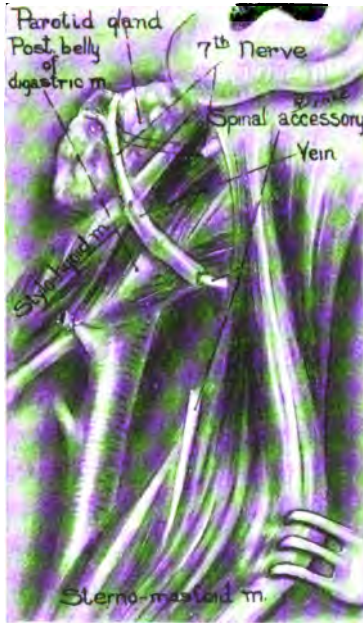


FIG. 451.—Anastomosis of the proximal end of the spinal accessory nerve to the distal end of the seventh nerve.

improvement in the patients benefited was 72 per cent of the sensory, motor, and trophic functions. Twenty per cent only of these patients were improved, in 30 per cent the results were indeterminate, and in 50 per cent they were failures. In one patient the wound became infected. There were no deaths.

Four external popliteal anastomoses were made, all on males, whose average age was thirty years; all have been heard from following operation. The average duration of injury was twelve months, the shortest eleven months, and the longest sixteen months. Three of the injuries

were associated with lacerated wounds, and one with dislocation of the fibula. Three operations were end-to-end anastomoses with silk, in which fascia was used as a covering, while the fourth was a plastic operation. The average time before improvement was noticed was eleven months; the average time before maximum improvement was reached was approximately twenty-four months. The average improvement obtained was 43 per cent return of the sensory, 30 per cent of the motor, and 80 per cent of trophic function. In one case the result was a failure, and in another the result was indefinite. The failure of regeneration in one case was due to an infection in the wound.

Two sciatic nerves were repaired. One patient was injured eight years before coming to the clinic; the time of injury of the other was not ascertained. The injury in one instance was due to a revolver bullet, in the other to a lacerated wound. Both operations were end-to-end anastomoses, one with silk and one with chromic catgut; fascia was used for covering in both cases. In the one case there was a gap of three-fourths of an inch between the nerve ends. The average time before improvement was noticed was six months; the average time until maximum improvement was reached was eighteen months. One of the 2 patients was heard from following operation; he reported 40 per cent return of the sensory, motor, and trophic functions.

One right recurrent laryngeal was anastomosed end-to-end one year after the injury. The patient was a male, aged thirty-nine years. The suture material used was not recorded. Improvement was first noticed twelve months after the operation; maximum improvement, 90 per cent return of the motor function, was reached at the end of thirty-six months.

#### GENERAL SUMMARY OF CLINICAL FINDINGS

Of the 41 patients operated on for nerve anastomosis, 35 were males and 6 were females. The average duration of injury was fifteen months. Seventy-three per cent of the patients have been under observation or have been heard from since the operation. Seven of the forty-one injuries were associated with fractures, one with a dislocated bone, and thirty-three with lacerated wounds. Eighty and five-tenths per cent of the operations were end-to-end anastomoses; the balance (19.5 per cent) were plastic operations of some sort. Sixty-five per cent of the forty-one anastomoses were sutured with silk, 29 per cent

with chromic catgut. Fascia alone or with silk and chromic catgut in the form of a tube was used to protect the anastomosis in 49 per cent, vein was used in 10 per cent, and in 10 per cent there was no covering. Seventy-three per cent of the anastomoses were in direct apposition, 27 per cent presented gaps varying from one-half to one and one-half inches in length, the average length being one inch. The average time before improvement was noticed was nine and nine-tenths months and the average time to reach maximum improvement was twenty-one and five-tenths months. The average amount of improvement obtained was 58 per cent return of the sensory, 62 per cent return of the motor, and 67 per cent return of the trophic function. Seventy-three and one-tenth per cent of all the patients operated on showed improvement, 17 per cent of the operations were total failures, and 9.7 per cent gave indefinite results. Four and eight-tenths per cent of all the wounds became infected. There were no operative deaths.

#### OPERATIVE FINDINGS

Three clinical conditions may be found at operation:

1. Complete severance of the nerve with retraction, and a neuroma on each end. The neuroma on the proximal end is usually about twice the normal size of the nerve, while the neuroma on the distal end is very small, only about one and one-fifth times the size of the normal nerve. The portion of the nerve below the distal neuroma is enlarged to about one and one-sixth times the normal size of the nerve; it is edematous and injected, and has a rather soft, mushy feel.

2. A diffuse and nodular thickening of the nerve, due to trauma. This occurs usually over some bony prominence; for example, a very common lesion is that found in the ulnar nerve, where it is situated over the inner condyle of the humerus, the anterior tibial, which passes around the head of the fibula. The proximal end of the nerve is normal in appearance and size, while the distal end is enlarged, œdematous and injected; the enlargement is about one and one-sixth times the size of a normal nerve. The nodular masses are pseudo-neuromas and histologically show an interstitial neuritis.

3. A condition due to constriction of the nerve, the most common example being the musculospiral nerve, which is strangulated by the callus which forms after a fracture of the humerus. The histories in



such cases are very significant in that the paralysis is progressive and comes on several weeks after the injury. The nerve proximal to the constriction is normal in appearance and size, while the portion distal to the constriction is frequently smaller than the normal nerve and not edematous nor injected unless the constriction is complete, when the appearance is the same as in the second group.

Paralysis of the seventh nerve may be caused by inflammatory processes or trauma; in either case surgery is indicated unless there is a spontaneous cure.

#### OPERATIVE TREATMENT

The ends of a severed nerve are retracted, generally, in the line of its original position. The ends are usually adherent to the mass of scar tissue, so that it is quite important to expose normal nerve above and below the scar, after which the ends should be freed by very gentle dissection. After the neuromas have been exposed all of the neuromatous scar tissue should be removed. The bleeding is usually controlled by allowing the cut ends of the nerve to come in contact with dry sponges for from five to ten minutes. If this is not sufficient, the vessel may be tied with fine catgut.

In anastomosing nerves the sutures are applied to the sheath (epineurium) surrounding the nerve. They are inserted obliquely into the sheath, thus bridging the gap with a cylinder of silk, of five or six strands, to the nerve. If the ends can be brought into apposition, no fascial covering is necessary. If there is much tension, fine silk is preferable to chromic catgut for suture material. When it becomes necessary to leave a gap between the nerve ends it is important that this gap should be covered by membrane or fascia. An apposition is preferable to a gap, as the prognosis is much better. It should be remembered that a nerve will stand gentle stretching and that the extremities may be flexed to relieve tension.

The surgical procedure in a traumatized nerve with neuroma depends on the amount of existing paralysis. If the paralysis is less than 50 per cent, the epineurium and perineurium are divided to liberate the normal nerve fibers, but if the paralysis is more than 50 per cent the neuroma is resected, exposing normal nerve fibers above and the definite nerve sheaths below; the ends are anastomosed in the same manner as when the nerve has been completely severed. This dis-

### GENERAL SUMMARY OF OPERATIVE RESULTS

[illegible]

NOTE.—19.5 per cent had plastic flap operations; 27 per cent had interaural gaps; 10 per cent were indeterminate; 80.5 per cent had end-to-end anastomoses; 73 per cent had no gap or were not reported; 17 per cent were failures; 73 per cent were improved; 62 per cent average degree of improvement.

tion is made on the basis that if there is 50 per cent function and further paralysis can be prevented, it is much better that the patient should be slightly handicapped than that the nerve should be resected and anastomosed with the chances of failure.

The surgical treatment of constricted nerves also depends on the amount of paralysis present. If the paralysis is less than 50 per cent, the nerve is freed from the surrounding scar tissue and protected by a cuff of fat and fascia. If the paralysis is more than 50 per cent, the constricted area is resected and anastomosed.

The surgical treatment of facial paralysis depends on the cause of the lesion, and it is better to wait a reasonable length of time after the injury (six months) before advising operative treatment, unless it can be determined that the nerve is completely severed, in which case operation should be undertaken as soon as the latent infection has cleared up. If at the end of six months there is no sign of regeneration, one of two courses may be followed: Anastomosing the distal end of the seventh nerve to the hypoglossal, or anastomosing it to the spinal accessory, preferably the latter.

#### SUMMARY

1. The regeneration of the peripheral nerves may be accomplished by nerve anastomoses.

2. The degree of regeneration depends on (1) duration of time between injury and repair (the shorter the period the greater the regeneration; the possibility of regeneration is very slight after three or four years), (2) actual loss of nerve tissue, and (3) retraction of severed ends.

3. In the technic of nerve repair (1) no covering is necessary if the freshened ends can be sutured in close apposition; (2) if an intervening gap remains it should be tubulized, preferably by fascia; (3) if the gap is longer than 5 cm. tendon transplantation and arthrodesis should be considered instead of nerve anastomosis; (4) autogenous transplants may be considered for short gaps, but they are of no greater value than tubulization; (5) in all technic, the wound should be free from hemorrhage and infection and the nerve ends should not be traumatized; and (6) during the postoperative convalescence, the paralyzed muscles should be massaged and passive motion should be administered.

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## CUTTING THE SENSORY ROOT OF THE GASSERIAN GANGLION FOR THE RELIEF OF TRIFACIAL NEURALGIA\*

A. W. ADSON

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The treatment of trifacial neuralgia has varied from the use of simple counterirritants to the most radical procedure, namely, ganglionectomy. The methods now employed are injection of alcohol into the peripheral branches of the ganglion, avulsion of the peripheral branches, and the division of the posterior root, known as the physiologic extirpation of the ganglion.

The disease has no known etiology. Sir Victor Horsley has stated that trifacial neuralgia is possibly caused by dental infection, resulting in ascending neuritis. This, however, has been objected to by numerous physicians on the grounds that if the condition were ascending neuritis, there would be a definite anesthesia as well as a motor paralysis in the branches involved. Frazier states that its etiology may be a sclerotic lesion of the ganglion, while Dana ascribes the probable cause to degenerative changes in the ganglion and nerves which lead to neuritis. These suggestions are at least hints toward solving the problem of the etiology.

Patrick, in his reviews, has given an excellent résumé of the symptomatology of trifacial neuralgia. He calls attention to the fact that the disease is about equally divided between both sexes, that there is only one type, that it usually occurs in middle life or after, but that it may occur in very young persons. He reports a case in which the symptoms began when the patient was 7, and 3 cases in which the patients were 75. Patrick's deductions are practically as follows: There are no predisposing factors, and while some patients are neurotic others are not. The disease is not hereditary although there are cases on record in which several members of the same family were afflicted. The neuralgia affects the infra-orbital division first in

\* Reprinted from Surg., Gynec. and Obst., 1919, xxix, 334-339.

the order of frequency, then the mandibular, and lastly the ophthalmic. Pain, as experienced by patients, is described as, "shooting, stabbing, jabbing, flash-like, darting, and zigzag lightning of the face;" it is, as a rule, of short duration, and not a continuous, dull, aching type that is usually brought on by irritation, such as eating or drinking of hot or cold foods and liquids, talking, exposure to sudden drafts, or washing the face and teeth. The patients complain of certain areas of the face, the trigger zones, being more sensitive than other parts of the face. Patrick also states that the disease is generally a chronic one, that he has seen no spontaneous cures, that quiescent periods may last from four to six months, that seasons have no bearing on the causation of the attacks, and, that during the attacks pain is usually quiescent at night. The condition has a definite symptomatology and does not simulate migraine nor pain that comes from sinus infection or dental caries. The true case of trifacial neuralgia has never been relieved by sinus drainage nor by the removal of teeth.

The first radical treatment was administered for the condition by Rose in April, 1890, when he removed the gasserian ganglion, but on account of the serious bleeding and the complications that developed, he was compelled to abandon this procedure. In 1898, Hutchinson advised a partial resection of the ganglion. He removed two-thirds of the ganglion and resected the second and third branches, saving the ophthalmic. His preference for this operation was on the grounds that it is not so serious as a complete ganglionectomy, that it does not produce anesthesia of the eye, thus avoiding conjunctivitis and trophic interstitial keratitis. This operation is at best attended with considerable bleeding and does not offer any relief for neuralgia of the ophthalmic branch.

Pitres and Verger, in 1902, and Schlösser, in 1903, described methods of injecting the peripheral branches of the fifth nerve with alcohol for the relief of trifacial neuralgia. Härtel described the technic for injecting the gasserian ganglion with alcohol, and since then numerous articles have appeared on the subject. The alcohol treatment is definitely indicated in a certain group of cases, assisting in the diagnosis by giving relief in the true trifacial neuralgia and relieving temporarily patients who are poor operative risks and patients who are being prepared for the radical operation. Alcohol injection of the peripheral branches is not satisfactory as a routine treatment because the condition offers only palliative relief; the

average time of relief afforded is nine months. The injection of the ganglion is a rather difficult procedure; extreme care must be exercised not to inject the brain stem. While the effects produced are more lasting than those from the injection of the peripheral branches, they are associated with more serious complications than is the present radical treatment of the posterior root. Härtel reported eye complications in 25 per cent of his series. Avulsion or torsion of the peripheral branches is practised by a number of physicians, but the relief is generally of shorter duration than the relief afforded by the injection of alcohol. Beckman stated that the average time of relief obtained from the injection of alcohol is eight and four-tenths months. While the operation is not attended with serious complications, it is very difficult to secure complete relief, and it is difficult to repeat.

Division of the root, or the physiologic extirpation of the ganglion, appears to be the operation of choice in the radical treatment of trifacial neuralgia. Attention was called to this treatment by Spiller in 1898, and by Frazier in 1901. In their experimental work they proved that if the fibers posterior to the ganglion are divided, regeneration never occurs in the brain stem. Following Frazier's and Spiller's work Van Gehuchten presented his investigation, which corroborated their work, and in 1918 Frazier reported a series of cases in which this technic had been employed with gratifying results.

The complications attending the various ganglion operations have been serious hemorrhages, paralysis of the third, fourth, and sixth cranial nerves, frequent paralysis of the frontal branch of the seventh nerve with occasional involvement of the entire seventh nerve, conjunctivitis, and trophic interstitial keratitis. The bleeding has been due to inability to control the venous hemorrhage, with occasional injury to the middle meningeal, but as better exposure of the ganglion has been obtained by the use of specially adapted retractors with lights, the bleeding can be controlled with very little difficulty. Frazier has called attention to the use of small pledgets of cotton made by cutting dental rolls into small cylinders. These are of great value in elevating the dura from the bone and can be used as tampons to control small venous oozing along the floor of the middle fossa; either the middle meningeal may be ligated or the foramen spinosum may be plugged with wax. The paralysis of the third, fourth, and sixth cranial nerves has been avoided by the use of the ganglion retractor, which keeps the



dura on tension and does not rest on the cavernous sinus or ocular nerves. The small dental packs also assist in avoiding this complication as they can be placed directly over the bleeding point, thus dispensing with a gauze pack, which occasionally produces paralysis. The frontal branch of the seventh nerve was frequently injured in making the Hartley-Krause incision, but it is rarely injured in the incision described by Frazier, which is within the hair-line.

In operating in 10 cases of trifacial neuralgia in 1917, and in 28 cases in 1918, at the Mayo Clinic, two complications have attended

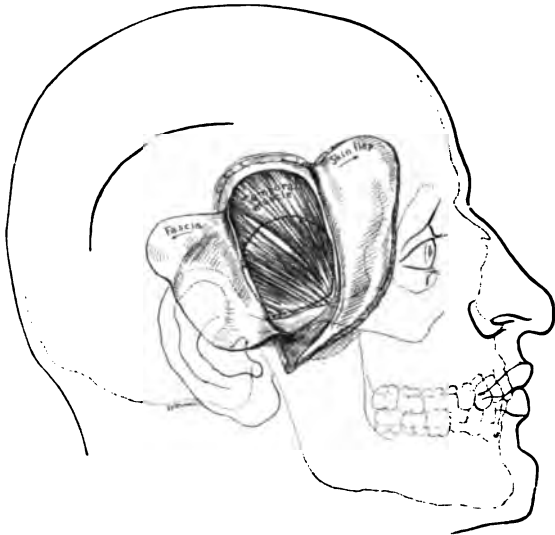


FIG. 452.—Diagram showing the approach to the ganglion. The skin flap is turned forward, the fascia flap backward, and the temporal muscle is split in the direction of its fibers. The decompression following is indicated by the heavy dotted line.

the technic suggested by Frazier and Spiller: the occasional paralysis of the seventh nerve, and the trophic interstitial keratitis. When seventh nerve palsy occurs, it is accompanied by a lagophthalmos which, in turn, permits undue exposure and dryness of the cornea, resulting in abrasions and the formation of trophic ulcers. Interstitial keratitis may occur independently of paralysis of the seventh nerve; it is very troublesome and may result in the formation of an opaque cornea. If these complications could be avoided in the technic, the operation could be recommended without any hesitancy to patients suffering with trifacial neuralgia.

In an investigation of the probable factors involved in the causation of seventh nerve palsy, it was found (Hutchinson) that the seventh nerve paralysis might occur as the result of detachment of the dura from the petrous bone, thus allowing the blood to enter into the small openings leading into the aqueduct of Fallopius; when the paralysis occurs, it occurs immediately. It may be only slight at first, but it becomes complete within a day or two, as in one of our patients. It was present immediately after the operation, progressed until complete, and then subsided, very slowly, during six months. The condition was

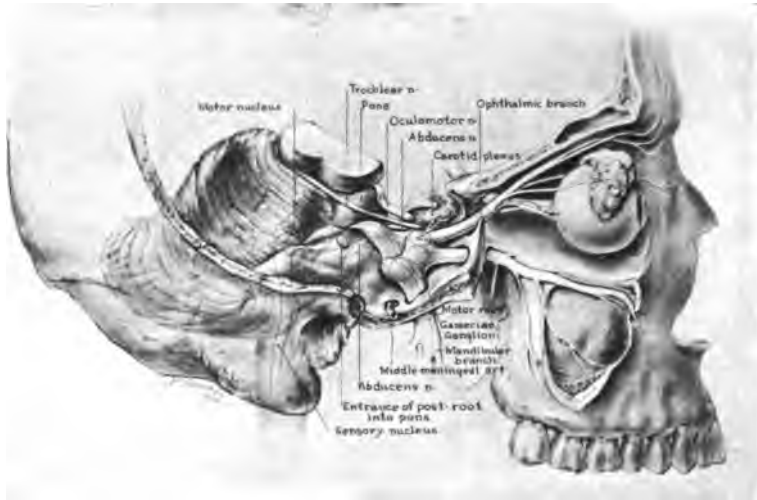


FIG. 453.—The relation of the ganglion to its surrounding structures and the communications between the carotid plexus and the ophthalmic portion of the ganglion.

also attended with trophic interstitial keratitis. A notation was made at the time of operation to the effect that the dura had been stripped along the ridge of the petrous bone. I have had 4 patients with a seventh nerve paralysis, however, in whom the dura was not stripped from the petrous bone. The technic employed was that suggested by Frazier and Spiller, in which the root was avulsed with a blunt hook. All of these patients were free from facial palsy until after the fifth day, when it came on gradually, became complete, remained for about six weeks, and then gradually disappeared. I am unable to say definitely just what the causal factors were, but, on avulsing the ganglion roots at postmortem, considerable trauma in the pons at the point of exit of the posterior root of the gasserian ganglion was noted.

It seems probable that the cause of occasional seventh nerve paralysis is trauma resulting in small hemorrhages and edema of the pons

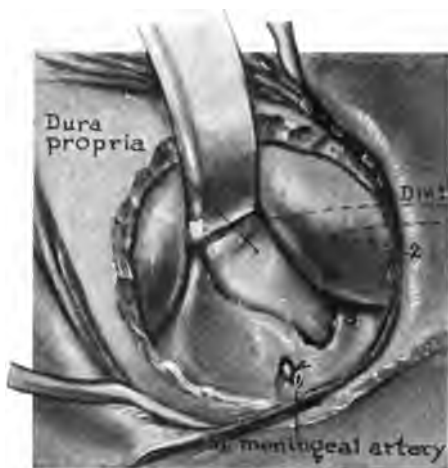


FIG. 454.—Exposure of the third branch of the right trigeminal nerve, gasserian ganglion and ligated middle meningeal artery.

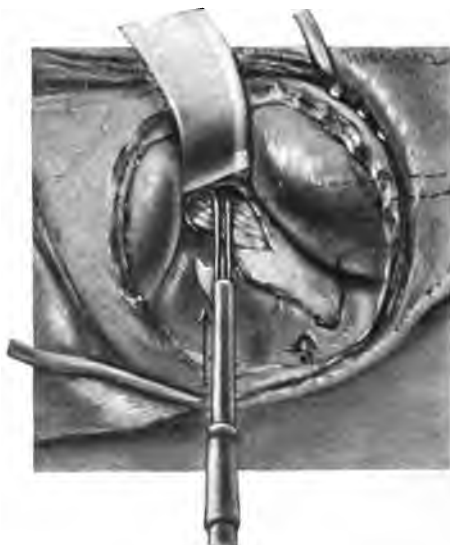


FIG. 455.—Posterior root brought into view after the division of the dura propria preparatory to cutting the posterior fibers.

and of the brain stem. This is further verified by the results obtained when the posterior root is cut and not avulsed. No seventh nerve

paralysis occurred in 26 successive cases from January to August, 1919, since this change was made in the technic.

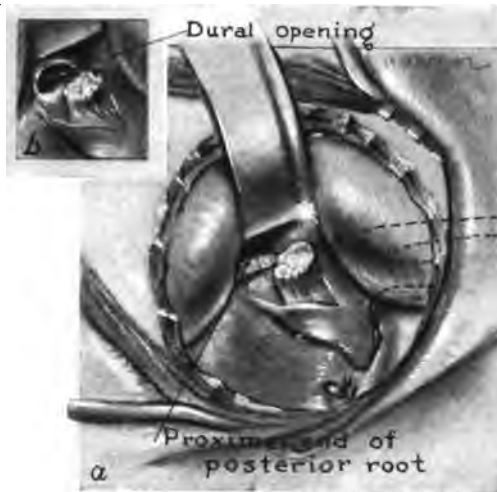


FIG. 456.—*a*. Cut ends of the posterior root of the gasserian ganglion. *b*. Dural foramen over petrous portion of temporal bone through which the proximal fibers of the posterior root have dropped into the posterior fossa.

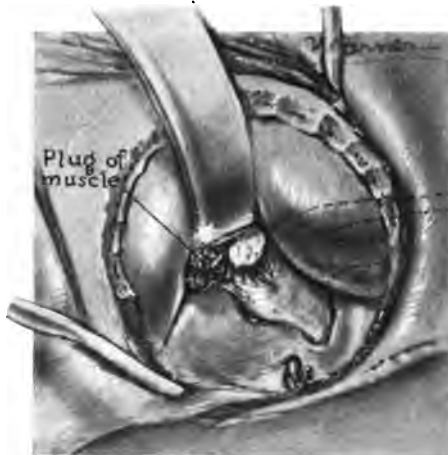


FIG. 457.—Inserting pledget of muscle into dural foramen between severed ends of the posterior root.

Budge's experimental work on dogs shows that the pupils of the eye will contract when the branches of the trigeminal nerve are divided

peripheral to the ganglion but will contract only slightly when divided proximal to it.

Bernard found that the pupil contracted and later dilated, after the division of the trigeminus, but never attained the same size as the pupil on the other side. These phenomena occur after central division as well as after peripheral division of the fifth nerve.

Spiller says that it is probable that sympathetic fibers pass to the eye after entering the trigeminal nerve through the gasserian ganglion and, as in the division of the sensory root, they are not injured; the danger of ocular disturbance by this operation is lessened. The trophic influence of the gasserian ganglion on the eye may possibly depend on the integrity of these sympathetic fibers.

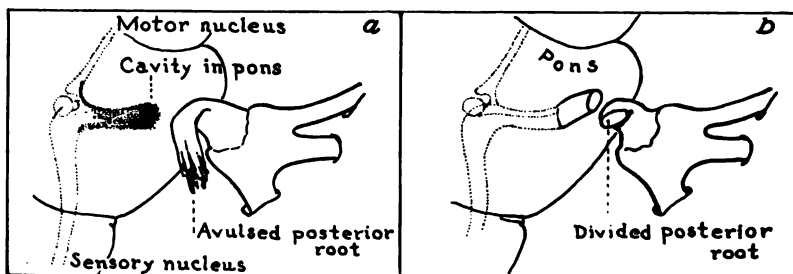


FIG. 458.—a. Trauma produced within the pons by avulsion. b. Division of the posterior root by cutting without causing trauma of the pons.

In our observations, it was found that whenever trophic interstitial keratitis occurred, one of two things happened at the time of operation; either the dura propria had been split so that the ganglion was greatly exposed or it was necessary to insert a large pack to control bleeding, thus causing pressure on the ganglion. It was noted also that if only the posterior margin and root were exposed, there was never any immediate keratitis. From experimental work it is evident that sympathetic fibers from the carotid plexus in dogs pass through the ganglion into the ophthalmic branch. It is difficult to state just what communications take place in man, but the pupillary phenomenon, as seen in dogs, does not occur in man. I believe, however, that sympathetic fibers play an important part in the trophic supply of the cornea, or that this function is controlled by the ganglion cells of the ophthalmic division, which, if not injured during the operation, will protect the cornea against ordinary irritations. The ganglion cells or sympathetic fibers remain uninjured if the dura is not elevated over the ganglion.

## OPERATION

The patient is placed in a semi-erect position with the head on a special headrest which may be raised or lowered to the position desired. A general anesthetic is used. The anterior limb of the question mark incision over the temporal region and down in front of the ear to the zygoma begins 3 cm. posterior to the external angle of the orbit and 3 cm. above a line drawn parallel with the zygoma. The skin flap is turned forward and the fascial flap covering the temporal muscle is turned backward, both being carried down to the zygoma. The temporal muscle is split and the skull exposed by a mastoid retractor. A subtemporal decompression is done, and an area of



FIG. 459.—(above). Guillotine knife.  
FIG. 460.—Ganglion retractor.

bone about 3 cm. by 3 cm. is removed. The dura is gently elevated from the middle fossa until the meningeal artery, which we prefer to ligate, is exposed. The foramen is plugged with bone wax followed by further elevation of the dura until the posterior margin of the third branch appears. Dissection is then carried posteriorly and inward, exposing only the posterior margin of the ganglion; the dura propria is not opened until the region of the posterior root is reached; thus injury of the ganglion is avoided, particularly of the inner portion, the cells controlling the ophthalmic branch. Before the dura propria is opened over the posterior root, all bleeding is controlled. The dura covering the brain is held under gentle tension and the cavity is well illuminated by means of the ganglion retractor. After the dura has been opened, the fibers of the posterior root are gently exposed and slightly elevated, and the guillotine knife is slipped over the fibers which are to be cut, thus avoiding any trauma of the

pons or brain stem. The cavernous sinus is rarely injured, inasmuch as all of the anatomic marks may be seen clearly. The fibers of the posterior root just above the ganglion are turned down over the ganglion while the proximal fibers are pushed back into the posterior fossa. A small pledget of muscle is inserted into the dural foramen as a plug. This assists in making a barrier between the severed ends and prevents the extensive loss of cerebrospinal fluid that usually follows when the patient recovers from the anesthetic. If there is any danger of bleeding, it is well to insert a narrow strip of iodoform gauze, and remove it on the third day. The muscle and fascia are closed with interrupted sutures of chromic catgut No. 1. The skin is closed with interrupted sutures of silk, which are removed on the fifth day. During the operation the eyelid is closed with adhesive, which is replaced by a Buller's shield before the patient leaves the operating room. The shield is worn for a week or ten days and subsequently is exchanged for close fitting automobile goggles, to be used whenever the patient is exposed to wind or dust. In addition to wearing goggles, we advise irrigations twice daily with 2 per cent boric acid solution.

The principles of the physiologic extirpation of the ganglion laid down by Spiller and Frazier have been carried out in the foregoing technic, except that the posterior root has been exposed without injury to the ganglion and particularly the cells supplying the ophthalmic branch, thus decreasing the frequency of trophic interstitial keratitis, and the posterior root is cut instead of avulsed, in this manner avoiding the occasional seventh nerve paralysis.

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## TECHNIC

'19—71



## EXPOSURE IN GALLBLADDER SURGERY\*

J. C. MASSON

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A review of the literature on the subject of surgery of the gallbladder makes it self-evident that the members of the medical profession have not all been of the same mind with regard to it. Early discussions all related to the desirability of removing or of merely draining the gallbladder. This contention is now fairly well settled, and the cases are few in which it is believed that the patient's best interests are served by a simple drainage operation. It must be admitted that cholecystostomy, in the hands of the casual operator, is a much easier and safer operation than cholecystectomy, but no one should attempt to remove gallstones who is not also able and prepared to do any operation on the biliary tract that may be found necessary. We all know how often complications are found when they are least expected, such as stones in the common duct or even fistula between the gallbladder and other organs.

Specific indications for the removal of the gallbladder or for drainage have been thoroughly discussed in medical journals in this country, and the list of indications for removal leaves very little question in the mind of the reader that the right thing to do when in doubt is to remove the organ. The remaining contention, therefore, between surgeons is with regard to the method of removal. A great many believe that removal from the fundus down is the safer procedure, in spite of the fact that the field of operation is more or less soiled with blood during the most important and dangerous part of the operation. I have frequently heard surgeons say that in operating on a thin person with a low-lying liver which is easily rotated into the wound, and with the field of operation practically outside the abdomen, it is a simple matter to remove a gallbladder by first cutting the cystic duct, but that they would like to see it done in a really difficult case, such as that of an acute gallbladder in an obese patient with a low costal arch.

\*Reprinted from *Ann. Surg.*, 1919, lxix, 423-425.

My own training has been almost entirely in doing cholecystectomies from below up.<sup>3</sup> I believe that I have had my share of experience in the emergency and acute varieties of cholecystitis with all the added handicaps of obesity and immobile livers, and I am satisfied that with the exposure it is possible to obtain in every case, the rational operation can be safely performed.

To be able to utilize all the exposure possible is, to my mind, an important consideration in surgery. I have never seen a surgeon in trouble while doing a thyroidectomy if he had the maximum amount of exposure, and we can all recall our occasional difficulties when attempts have been made to remove an appendix through a button-hole incision; this is also true in operations on the biliary tract. A method that I have used during the past year, which helps in the more difficult cases to visualize the neck of the gallbladder, the cystic duct and artery, and their relations to the common duct and the duodenum, is as follows:

#### TECHNIC

The abdominal incision extends from the midline at the tip of the ensiform to a point about 2 inches external to the umbilicus. If it is necessary to remove the appendix the incision may be extended downward, especially if there is an excessive amount of subcutaneous tissue. When not contra-indicated the usual exploration is made. The stomach, large bowel, omentum, and small intestine are separated from the field of operation by three or four abdominal sponges, held in place by the left hand of an assistant. It is important when once the sponges are in place that the assistant should not move this hand during the operation. In almost all such cases this exposure is all that is needed, even when the right lobe of the liver cannot be rotated. In the exceptional case, however, additional exposure is obtained by inserting a pack (4 inches by 3 feet) between the posterior-superior surface of the right lobe of the liver and the diaphragm (Fig. 461). In this manner the liver is made to descend slightly, the concave visceral surface is flattened somewhat, and the hilum of the liver is made more accessible. The insertion of this pack is an easy matter and if carefully placed it can in no way injure either the liver or the diaphragm. With an ordinary abdominal retractor the second assistant retracts the right costal margin upward and outward, while with a long shoe-horn retractor the first assistant gently retracts the

liver in the opposite direction. The operator is now able to place the pack in position by using a pair of 9-inch tissue forceps, carrying



FIG. 461.—Inserting pack between liver and diaphragm.

the gauze along the shoe-horn retractor. Figure 462 shows the final exposure. I have used this procedure in numerous cholecystectomies, and am satisfied that it has frequently made very difficult cases absolutely safe.

Injuries to the hepatic or common ducts, or hemorrhage, are always avoidable if the operator can see what he is doing and if he proceeds carefully. As anomalies of both ducts and blood-vessels

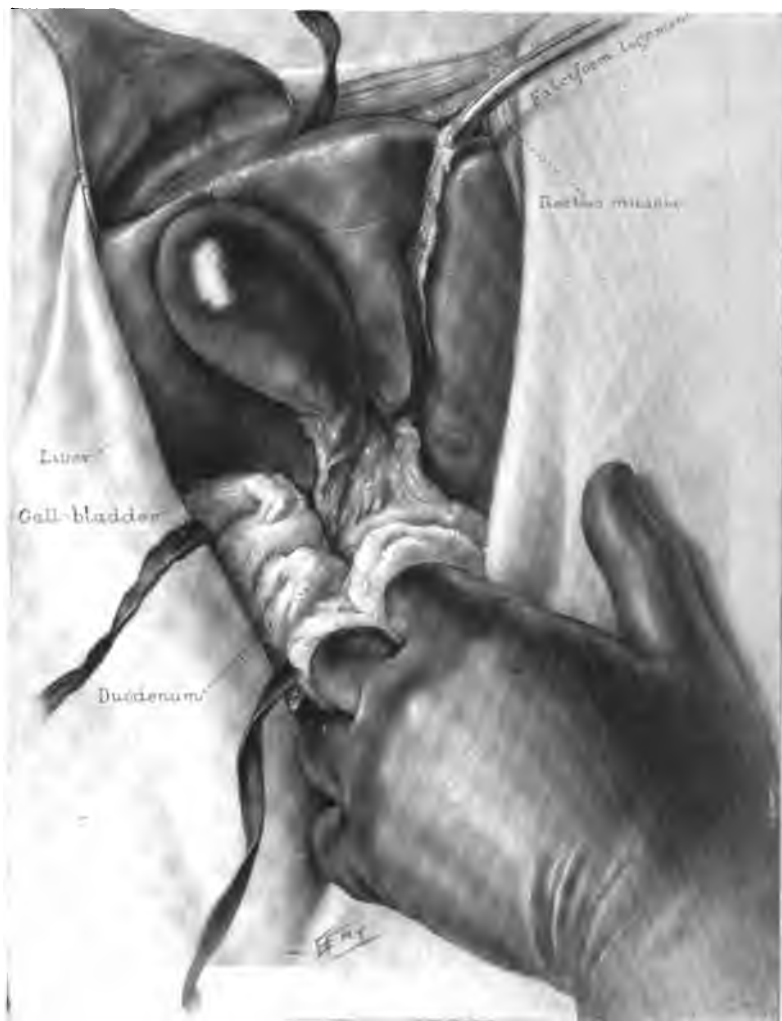


FIG. 462.—Final exposure, showing flattening of visceral surface of liver.

are very common, to know the text-book anatomy of this region is not sufficient.<sup>1, 2</sup> Absolute knowledge of what is in each forceps before it is clamped is necessary to safety in the procedure.

In cases of large, tense gallbladders it is often advisable first to empty the gallbladder with a trocar, and then to apply a 6-inch curved forceps to the fundus and another to the ampulla where it overlies the common duct. By drawing on the forceps, especially the last one, the cystic duct is stretched, and by a little blunt dissection with a pair of 7-inch curved forceps, it may be isolated and exposed throughout its entire length. Before cutting this duct the common duct should be palpated; it is much easier to do this now than later, as it can be steadied by traction on the forceps attached to the ampulla. The cystic duct and the artery are secured separately and ligated with plain catgut; care is taken to occlude the duct close to its juncture with the common bile duct and not to leave a pouch to be a possible cause of future trouble. If the common duct warrants exploration it is preferable to make the incision sufficiently long rather than attempt investigation through the open end of the cystic duct, which is frequently very unsatisfactory. With the mode of exposure herein outlined, all these procedures may be safely and quickly executed.

I believe that in the future I shall remove very few gallbladders by commencing at the fundus. I realize, however, that each case must be judged by itself, and that the steps of an operation should not be decided on until exploration has been completed. In the occasional case it may be difficult to expose the cystic duct and artery. I would then advise commencing the removal at the fundus.

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## AN EXTRA TAG ON THE ABDOMINAL SPONGE\*

J. C. MASSON

The dramatic manner in which sponges are counted after each operation, in some hospitals, is evidence of the fact that "accidents still happen." It is quite probable that more medicolegal cases come to trial because something has been left in the operative field than because too much has been taken out of it.

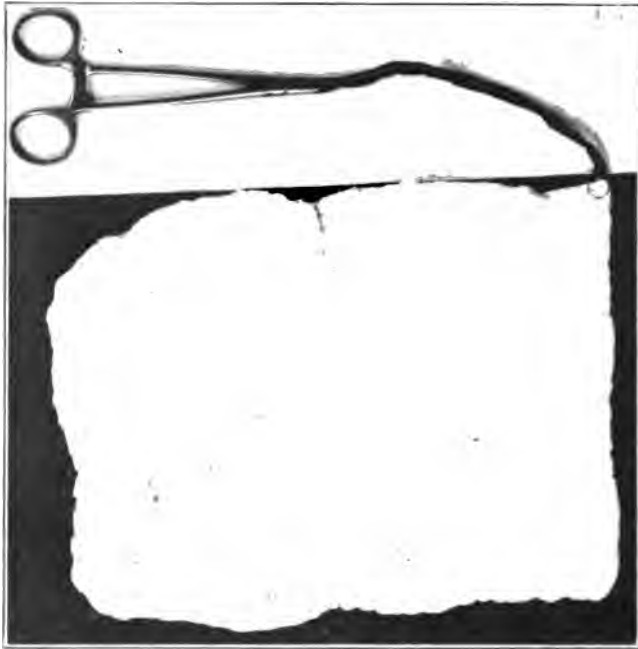


FIG. 463.—Abdominal sponge with ring attached.

Approximately 27,250 abdominal operations have been done at the Mayo Clinic within the last five years, and thirteen were for the removal of sponges. In most of these 13 cases the patients came from rural districts, and had been operated on for acute conditions by general practitioners who probably had had very mediocre

\* Reprinted from Jour. Am. Med. Assn., 1919, lxxii, 1612-1613.

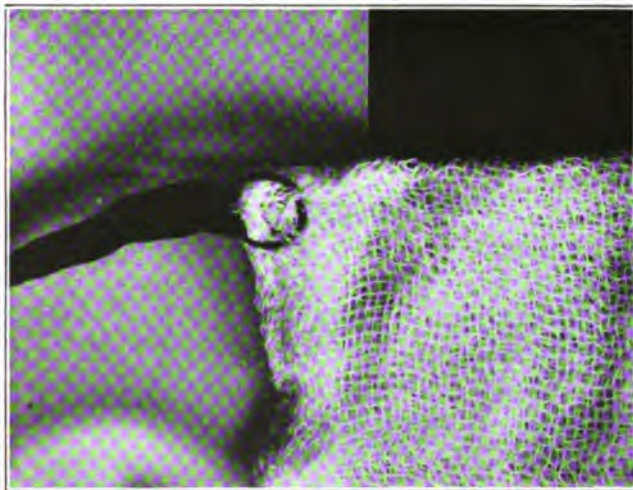


FIG. 464.—Abominal sponge with ring attached.

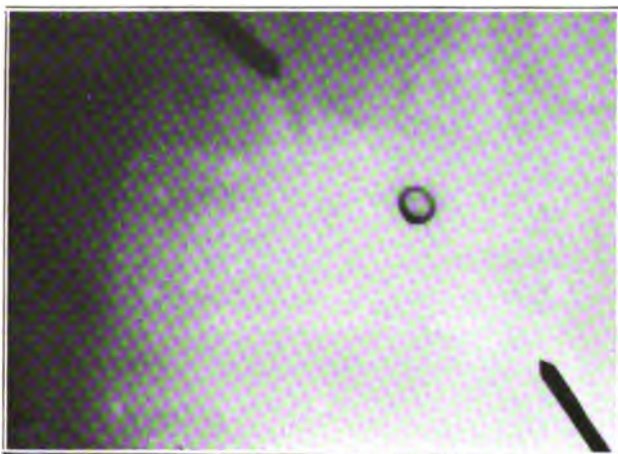


FIG. 465.—Roentgenogram showing sponge through a 200-pound patient.

assistance and were further handicapped by the confusion attendant at such operations. The only wonder is that such accidents do not happen more often in this kind of surgery. After a more or less stormy convalescence, the patient recovers from the operation; but he is left with a persistent sinus, and while he has the original operator to thank for having saved his life, if he learns that a sponge has been left in the wound and is the cause of the sinus, he will seldom hesitate to enter action for unlimited damages.

With a view to the special marking of all abdominal sponges, I have them made with a metal ring placed around the base of the tape and firmly sewed to both sponge and tape with strong thread. If a sponge is reported missing, the abdomen may be roentgenographed before it is reopened; the presence of the sponge will be revealed by the metal band. In hospital practice this procedure should be especially applicable, since if after a morning's work a sponge is reported missing and any one of two or three patients may be the unfortunate retainer, roentgenograms may be taken of all of them, and thus a difficult situation is cleared up with a minimum amount of trouble.

## A METHOD FOR THE PREPARATION OF PROPHYLACTIC AND AUTOGENOUS LIPOVACCINES\*

E. C. ROSENOW AND A. E. OSTERBERG

In prophylactic inoculations with a mixed vaccine against influenza and its complications, it was noted that a small percentage of the persons inoculated developed rather severe reactions.<sup>1</sup> The possible advantages to be derived by suspending the bacteria in oil, especially when a mixed vaccine is indicated, as first practiced by Le Moignic and Pinoy and studied on a large scale by Whitmore and his coworkers in the Army Medical School have been pointed out in a preliminary report. Owing to the slow absorption and the fact that bacterial toxins are lipotropic, larger doses may be given with less local and constitutional reaction than when the bacteria are suspended in salt solution. The formation of antibodies should be more marked and the resulting immunity more enduring.

The chief difficulty encountered in the preparation of a lipovaccine arises from the fact that the bacteria must be dried, and all methods used thus far for drying produce a clumping of the bacteria. This makes it necessary to break up the masses formed in the drying process before a homogeneous mixture in oil can be made. The method as worked out at the Army Medical School<sup>2</sup> consists essentially in drying the collected bacteria in Petri dishes at a relatively low temperature (53 C.), which inevitably causes them to clump in a firm, hard mass. They are then separated by prolonged grinding in bottles containing steel shot. This requires cumbersome and expensive apparatus and involves a number of steps in which contamination is prevented with difficulty. The method is obviously impracticable for the preparation of autogenous vaccines. The possibility that the prolonged grinding may render the bacterial substance more readily absorbable is also an apparent objection.

We have tried various procedures in order to simplify the methods used. In connection with some work in poliomyelitis it was noted

\* Reprinted from Jour. Am. Med. Assn., 1919, lxxiii, 87-91.

that streptococci and pneumococci not only remained Gram-positive but also retained specific immunologic characteristics for many months when suspended in 50 per cent glycerol. The dehydrating power of pure glycerol is well known, and it was thought that this might be an effective agent in drying the bacteria and in preserving their antigenic properties. But glycerol and oil will not mix, even when emulsifying agents are used, and hence this method was found impracticable. Drying the bacteria with absolute alcohol and ether or with acetone and ether, in which the bacteria are less solidly packed than when dried by heat, was thought of, but the possibility of destroying the antigenic properties would not justify the slight advantage gained, since the grinding process would still be necessary. The method of drying the frozen bacteria in vacuo is difficult, requires special apparatus, and does not eliminate the grinding process. The method of drying serums and other liquids at a low temperature in vacuo, as used by Burrows and Cohn, and by Marmier, was suggested by Dr. E. C. Kendall. This was found to be effective in getting rid of the water in a closed system and undoubtedly in preserving antigenic properties, but the grinding process was still found necessary. It occurred to us that if the water were removed by distillation in vacuo from a water-bacterial-oil emulsion, the oil would prevent the clumping of the bacteria and thus make the cumbersome, time-consuming, and otherwise objectionable grinding process unnecessary. With this as the underlying principle, a method has been developed for the preparation of varying quantities of lipovaccines.

#### METHOD EMPLOYED

The steps in the preparation of large quantities of oil vaccines may thus be subdivided:

1. The method for the preparation of the bacterial paste is identical with that used in the preparation of saline vaccine. The bacterial growth contained in glucose broth is centrifugalized out, the continuous feed centrifuge being used.

2. The bacterial paste is removed from the centrifuge bowl under a hood by the use of a spatula, and is transferred to the proper sized, wide-mouth bottle.

Sufficient sterile water is added to give a very dense but homogeneous suspension, and the mixture is thoroughly shaken. One cubic centimeter of water to each liter of broth-culture medium gives about the correct degree of concentration. The bacteria suspended in water are killed by thermal or chemical means. If heat is used, the bottle is immersed in a water bath and kept at a temperature of 60°C. for one-half hour, at the end of which time cultures are made. If a chemical method is to be used, sufficient cresol is added to the water suspension to make it a 2 per cent cresol solution. The mixture is well

shaken. After it has stood for twelve hours, cultures are made. In the case of *Staphylococcus aureus* and of other resistant bacteria, heat and cresol are used in combination. The suspension is heated for one-half hour at 60°C. in a 2 per cent solution, and then allowed to stand for twelve hours or longer.\* When the cultures prove sterile, the dense water-bacterial suspension is transferred to a proper-sized, round-bottom flask. We use the heavy Pyrex flask and have found it very satisfactory. For the preparation of large amounts of vaccine, for instance using the growth from 200 to 300 liters of glucose broth averaging 2 millions of bacteria per cubic centimeter, we ordinarily use a 3-liter flask. For smaller amounts a 2 or a 1-liter flask may be substituted. It is desirable, however, to use one of fairly large capacity because of the increased amount of surface obtained for the subsequent removal of the water in vacuo.

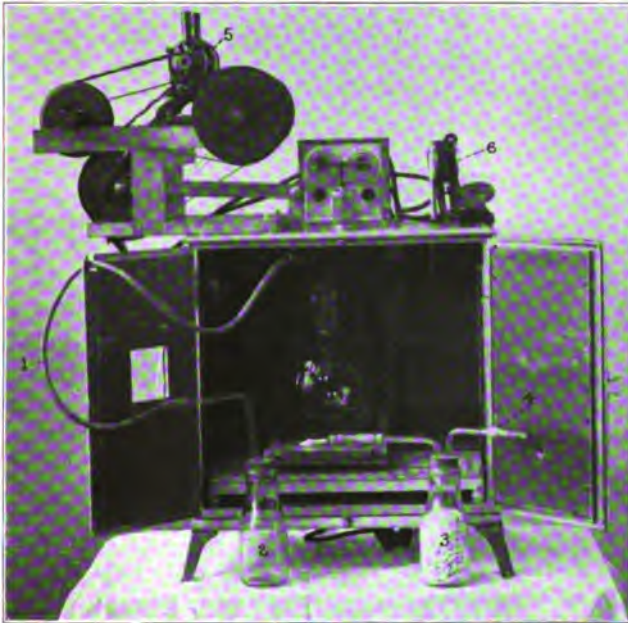


FIG. 466.—Oven and shaking machine.

3. For each liter of broth culture, 5 c.c. of sterile cottonseed oil, containing from 5 to 10 per cent lanolin, are added to the water suspension. To facilitate boiling and to aid in breaking up any bacterial clumps which may form, about 100 gm. of solid glass beads (3 mm. in diameter) or steel shot, three-thirty-seconds inch in diameter,† are added, and the flask is placed in the oven, as shown in Figure 466. Glass beads obviate any oxidase reaction which, in the case of steel shot, may result in a darkening of the suspension. The oven is maintained at a temperature of from 60° to 65°C. The

\* Sterilization in cresol is more effective at 37°C. than at room or icebox temperatures. Suspensions accidentally contaminated with *Bacillus subtilis* are rendered sterile when incubated at 37°C. for from twenty-four to forty-eight hours, while the control suspensions at the lower temperatures continue to show living bacteria.

† Hoover Steel Ball Company, Ann Arbor, Mich.:  $\frac{3}{32}$  inch diameter, steel burnishing balls.

oven and shaking machine, although convenient, are not essential. Numerous large batches have been evaporated by immersing the flask in a water bath at 65°C., and shaking it by hand at intervals. The flask is connected by flexible pressure tubing (1) to the condensing bottles (2 and 3), the first bottle serving as a condensing reservoir, and the second containing unslaked lime or calcium chlorid, which acts as a further drying agent. The parts sterilized include the flask, Tube 1 and Bottle 2. Tube 4 connects with the vacuum pump. The Geryk type of pump is used to develop a vacuum of 1 mm. or less of mercury. The rate of shaking is controlled by the small sewing machine motor (5) and the rheostat (6). The length of the stroke is 4 inches. Good agitation is obtained by using eighty strokes per minute. The time necessary to drive off completely all the water depends, of course, on the total volume present. From four to six hours ordinarily suffice for quantities requiring the removal of 150 c.c. or so of water. This length of time is proportionately decreased as smaller volumes of water are used. Until the water is practically all removed, the temperature of the evaporating liquid is from 10 to 15 degrees lower than that of the oven. The distillation requires little or no attention, the apparatus running very smoothly. As the mixture becomes more anhydrous, the viscosity is increased, and the suspension appears as a very thick emulsion when the major portion of the water is removed. As the last portions of water are driven off, the bacterial mass becomes solvated, forming a thick, nearly clear homogeneous suspension. It is important that all of the water shall be removed. The end-point of the distillation may be determined by the almost complete clearing of the mixture and the absence of water condensation in the condensing tube. The vacuum pump is disconnected at the cotton plug in Tube 4. The sterile cotton plug between Bottles 2 and 3 prevents contamination by the in-rushing air. The contents are poured through a fine mesh screen into a stock bottle in order to remove any pieces of cork or clumps of bacteria that may not have been broken up. To prevent any material loss of suspension, the flask may be washed out with small quantities of sterile oil.

4. For use as a vaccine, 1 c.c. of the stock suspension is diluted so as to give a final concentration of 50 billions of bacteria per cubic centimeter. For example, in the procedure just described, 5 c.c. of cottonseed oil are added to the growth from each liter of broth culture, representing 2,000 billion bacteria. Thus the stock suspension contains 400 billions of bacteria per cubic centimeter. This is diluted eight times, giving a concentration of 50 billions of bacteria per cubic centimeter for use as a vaccine. We prefer to base our dosage on bacterial counts rather than on the basis of weight of the bacterial substance. The percentage of error in weighing the dried bacterial substance, containing a variable amount of the precipitate formed in glucose broth as the result of acid produced during bacterial growth, is comparable with the experimental error made in counting bacteria. Moreover, it is difficult to avoid contamination in weighing the dried bacterial substance. If, however, the weight of the dried bacterial substance is desired when large amounts are dealt with, it may readily be obtained by subtracting the weight of the oil used from the total weight of the oil-bacterial suspension as removed from the flask at the end of the distillation.

5. The cottonseed oil and lanolin are sterilized in the autoclave at 15 pounds pressure for thirty minutes, and then removed while hot and placed in a hot-air oven at 105°C. for an additional thirty minutes, or longer if one is dealing with larger quantities. The flasks should be of the wide-mouth type of facilitate the entrance of steam; they should be filled well to the top and stoppered with a cotton plug. This sterilization, together with the removal of the oil from the autoclave while hot, reduces to a minimum the amount of water taken up. Heating in the air oven insures sterilization and re-

moves what water has been taken up by the oil. Contrary to the general opinion with respect to the difficulties encountered in sterilizing oil, we have experienced no difficulty by using this method. Control tests, in which the oil was contaminated with dust containing highly resistant spores, were found sterile in every instance, after using the foregoing method of sterilization. Because of the absence of water, the need for a preservative in lipovaccines is less than in saline vaccines. Various preservatives, such as camphor and chlorbutanol, have been used. In this method the small amount of cresol present in the stock suspension is sufficient to prevent bacterial growth from accidental contamination.

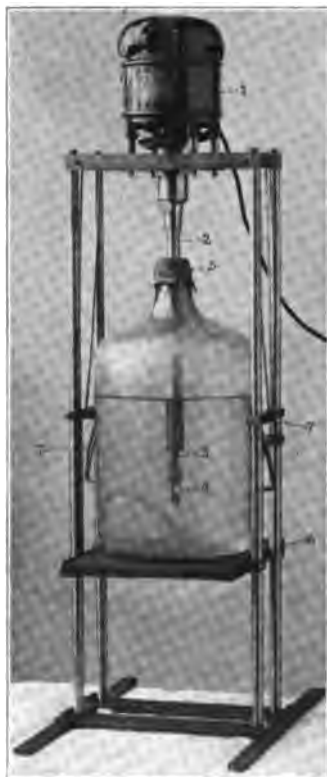


FIG. 467.—Machine for mixing the stock suspension with oil.

6. In order to insure complete sterility of the final vaccine, rigorous sterility tests are made (1) of the water suspension of the bacteria after the cresol and heat have been used; (2) of the cottonseed oil containing lanolin which is added to the water suspension; (3) of the stock suspension after distilling off the water, and (4) of the final oil suspension to be used as a vaccine. The cultures are made on blood agar in tall tubes of glucose-brain broth and litmus milk. In addition, the final product is injected into animals to insure sterility.

In order thoroughly to mix large quantities of the stock suspension with the oil for final use, the machine constructed for us by Mr. Little, is found convenient (Fig. 467). It consists of a vertical, one-eighth horse-power motor (Fig. 467, 1) fitted with a remov-



able sleeve (2) which contains bearings for the shaft (3), to which are fastened two propeller blades (4). These are thrown out horizontally as the shaft revolves at a rapid rate (1,700 revolutions per minute). The sleeve and shaft slip off together; these are sterilized and introduced through the small hole in the rubber dam (5). The support (6) is adjustable and is held securely in place by the hooks (7). The bottle, which has a capacity of 5 gallons, is filled three-fourths full. Smaller bottles may be used as required. The revolving blades are placed so as to produce a vigorous downward and outward current; hence the agitation is violent and soon results in an even mixture.

#### COMMENT

This method has given perfectly even, homogeneous suspensions with various species of bacteria. Large quantities of the mixed vaccine used for prophylactic inoculation against influenza, containing type pneumococci, Group IV pneumococci, green-producing streptococci, hemolytic streptococci and staphylococci, have been prepared by mixing in the centrifugal bowl the bacteria grown separately, as well as by mixing the dried oil suspensions of the different strains. In addition, excellent lipovaccines have been made of typhoid-paratyphoid and dysentery bacilli, of influenza bacilli, colon bacilli, *Streptococcus viridans* from endocarditis, gonococci and meningococci. The antigenic and toxic properties, especially in varying the doses of the mixed vaccine for influenza, will be reported in detail later. It is sufficient to state here that as high as 90 billions of bacteria have been given to a few persons, with only slight constitutional and local reaction. A dose of 0.5 c.c. containing 25 billions of the dried bacteria in the oil given more than 500 persons during a recrudescence of influenza rarely produced more than a slight reaction. But after the use of this vaccine, as after the use of the saline vaccine, an occasional person reacted more severely and a sterile abscess formed. Antibody production—agglutinins—has been found pronounced following the injections of such dosage. It is therefore evident that the somewhat prolonged heating in the oil in vacuo when large quantities are prepared does not destroy the antigenic properties.

It is imperative that there shall be no living bacteria in the water suspension at the time the oil is added. Early in the work it was thought that heating during the distillation in vacuo would serve the double purpose of killing the bacteria and driving off the water. This was found not to be so. Many of the suspensions showed living streptococci and other bacteria after prolonged heating at temperatures from 60 to 75° C. Temperatures as high as 100° C. for a period of two

hours failed to kill after the water had been removed.\* It is obvious that the mixture must be sterile at the time the oil is added. The heat used in the distillation does not alter materially the antigenic properties of the bacteria since it is not even sufficient to kill them. On the basis of this fact, moreover, there is good reason to believe that heating the water-bacterial-oil emulsion to the boiling point of water under atmospheric pressure will not destroy the antigenic properties of the bacteria. Should this be found to be the case the method might be simplified still further.

It is desirable in order to decrease the toxicity of the vaccine that the distillation shall be continued until the suspension has become cleared. This is well indicated in the following experiment: Two parallel series of persons—six in each series—were inoculated with equivalent doses of the mixed vaccine as used for prophylactic inoculation against influenza. One series received the incompletely dried, turbid suspension; the other the more completely dried and cleared suspension. Two persons in each series received each, respectively, 25 billions, 50 billions, and 75 billions of bacteria subcutaneously. The results showed that the incompletely dried suspension was decidedly more toxic, producing more reaction, both constitutionally and locally, especially locally, than the completely dried suspension. There was no fever nor other evidence of constitutional reaction in any who received the latter. This decreased toxicity is apparently due to a detoxicating action of the oil or lanolin as it permeates the bacterial substance or to a delayed absorption, or both.

The clearing that occurs as the oil permeates the dried bacteria is so striking as to suggest actual solution; but this is not what takes place, since the bacteria, on making a watery suspension from the oil, stain normally and are of sharp outline.

It has been found that the oil will not permeate bacteria dried in air in the usual way as completely as those dried in vacuo in the presence of oil. The toxicity of the former should, according to the foregoing experiment, be proportionately greater.

\* This observation suggested at once the possibility that bacteria might live in latency for a long time when dried in vacuo in oil. Strains of many species of bacteria have been filed away and are being studied as to viability and antigenic properties. Both viability and specific immunologic properties of some have been retained for months. Also the present method for immunization against rabies might be greatly simplified if the dried virus (rabbit cord) were suspended in oil. The further results will be reported later.

It may be suggested that desensitization against pollen or other protein substances may be greatly enhanced by the use of an oil instead of a saline suspension.

#### PREPARATION OF AUTOGENOUS LIPOVACCINES

The common 6-ounce nursing bottle shown in Figure 468 has been found useful for the preparation of autogenous lipovaccines. It



FIG. 468.—Flasks used for the vacuum distillation of water from water-bacterial-oil emulsion.

serves admirably as a culture flask, centrifuge tube, and vacuum flask. The bacteria are grown in tall columns of glucose broth (150 c.c. per bottle) for twenty-four hours, centrifugalized, the supernatant clear broth decanted, and the sediment suspended in 10 c.c. of a 1.5 per cent solution of purified cresol in water or salt solution. This is thoroughly mixed and placed at 37 C., for from two to fifteen hours,

when cultures are made. Streptococci and pneumococci are usually killed in from two to twenty-four hours. As soon as the suspension is found to be sterile it is centrifugalized; the supernatant fluid is decanted, and 6 c.c. of cottonseed oil containing 2 per cent anhydrous lanolin and a number of sterile glass beads or steel shot are added. The mixture is emulsified by being shaken for a short time. The small amount of water from this water-bacterial-oil suspension is now removed by applying the vacuum and immersing the bottom of the bottle in water heated to 60 C. By means of vigorous shaking at intervals the removal of the water is hastened. The vacuum and the heat are applied until bubbling ceases and the mixture becomes clear. The time required depends on the completeness of the vacuum and the amount of water to be removed, but the clearing usually takes place in from twenty minutes to one hour. The ordinary bacteriologic test tube as shown in Figure 468 may be used for the preparation of still smaller amounts, but for most purposes the bottle is to be preferred. If larger amounts of bacteria are required, the water or salt solution suspensions of a number of bottles are placed in one, and a correspondingly larger amount of oil is added. By the use of Y tubes the water from a series of suspensions may be removed at one time.

If, for example, bacteria such as influenza bacilli, gonococci,<sup>1</sup> and meningococci, which grow better on solid mediums, are to be used, the growth should be scraped together and washed off with salt solution so that the final suspension is roughly equivalent to that containing the bacteria from the broth culture. Sterilization and the further steps are carried out as above. In the case of the more resistant bacteria, such as staphylococci and paratyphoid bacilli, heating the cresolized suspension to 60 C. for one hour hastens the sterilization. The final bacterial content of the lipovaccine is calculated on the basis of counts made of the bacteria suspended in salt solution or on the basis of the total number of bacteria per cubic centimeter of broth culture. In the broth used in our laboratories, the amount of growth of pneumococci and streptococci is usually about 2 billions and the vaccine is made to contain approximately 50 billions of these organisms per cubic centimeter. The number of bacteria in the oil may be increased ten or twenty fold without interfering materially with the evaporation of the water or with the even distribution of the bacteria.

The value of autogenous lipovaccines in the treatment of various diseases is now being studied. Striking cures have been noted fol-

lowing the administration of a single large dose of staphylococci (80 billions) in severe recurring furunculosis. Benefit has followed the administration of autogenous pneumococcus and staphylococcus lipovaccines in infections of the maxillary sinus. Judging by the slight constitutional reactions, even when huge doses are given, and the improvement in the few cases studied, it would seem that much good might come from the use of autogenous lipovaccines, especially in the treatment of chronic or recurring infections, when a prolonged immunization is indicated. Marked benefit, it would seem, might come from the use of autogenous lipovaccines in diseases due to focal infection, particularly if foci are removed and the vaccine is made to contain the specific microorganisms as isolated from the focus.

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## HEAD RESTS FOR NEUROLOGIC OPERATIONS\*

A. W. ADSON AND G. G. LITTLE

### THE CEREBELLAR HEAD REST

The cerebellar head rest serves two distinct purposes: First, it holds the head in a prone position so that it can be tilted at all angles, thus giving good exposure of the cerebellum and cervical spine.



FIG. 469.—Cerebellar head rest, illustrating head piece and ether mask.

Second, it is arranged so that the jaw can be moved freely, the nose and mouth are exposed, and an adjustable ether mask can be attached to the frame to enable the administration of ether by the inhalation method without difficulty. The administration of intrapharyngeal

\* Reprinted from Jour. Am. Med. Assn., 1919, lxxiii, 182-183.

or intratracheal anesthesia is also made possible by removing the mask and inserting the intrapharyngeal or intratracheal catheter and attaching it to the anesthetic machine.



FIG. 470.—Cerebellar head rest; head in position, with ether masks removed, exposing the nose, mouth, and chin.

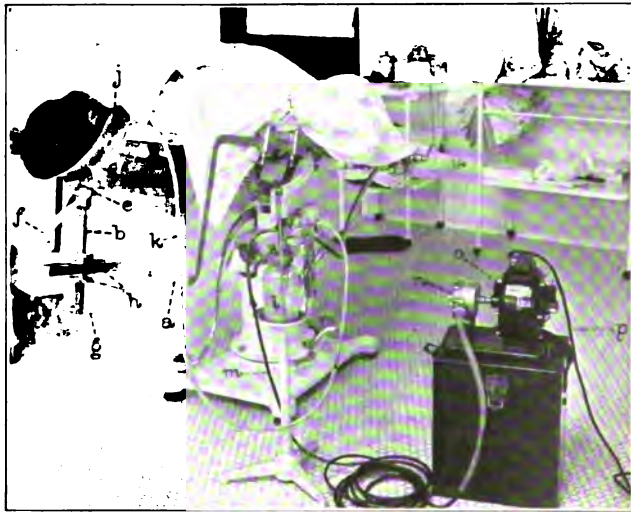


FIG. 471.—Cerebellar head rest; head in position, and ether mask attached and connected with the anesthetic machine and blower.

The ether mask (Fig. 469 *d*) is easily adjusted; it is secured in position by the curved edges, *j*. A short tube permanently fixed

to the mask provides a means of attaching the ether tube, *k*. It also directs the flow of ether toward the center of the mask.

The headpiece (Fig. 470 *c*) is secured to a ball pivot and may be tipped at any angle. It may also be moved toward or away from the table along the supporting frame, *a*, by loosening the threaded collars, *h*, which, when tightened, hold the headpiece at the required height.

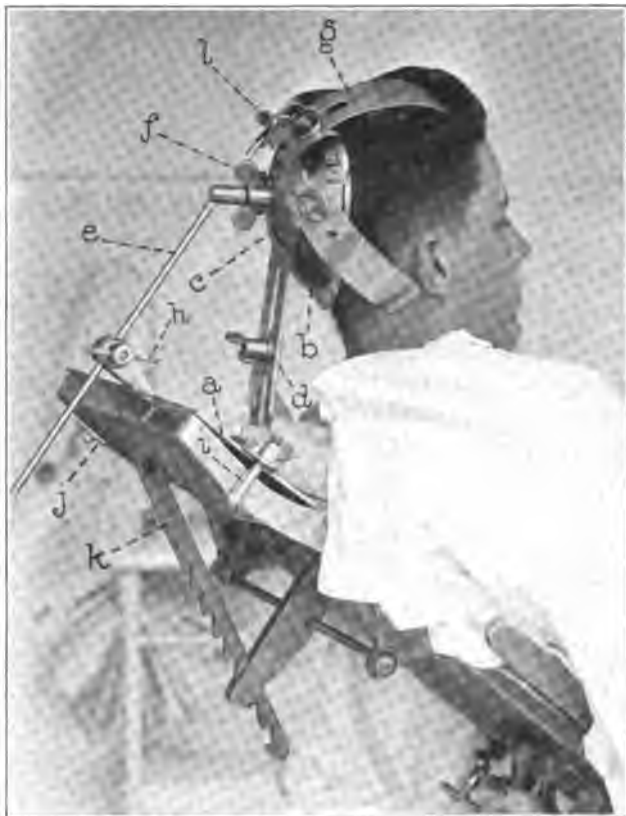


FIG. 472.—Ganglion head rest, illustrating its attachment to the swing leaf of the Balfour table, with the various adjustments.

The headpiece is locked to the standard, *b*, by tightening the collar, *e*, by means of the handle, *f*.

The supporting frame, *a*, is attached to the Balfour operating table; it is secured by a clamp, *i*; the swing leaf, *x*, of the table is lowered. The headpiece, having been formed to fit the forehead and cheeks, provides a comfortable rest for the patient's head, and leaves



the nose and mouth uncovered except for the detachable ether mask; the anesthetist is thus permitted free access to the patient's mouth.

The head rest and frame are attached to the operating table and connected by a flexible tube to the etherizing apparatus (Fig. 471 *l*); this is supplied with air from the motor-driven pump, *n*, through the flexible tube, *m*; the motor cord, *p*, plugs into a standard lamp socket.

#### THE GANGLION HEAD REST

The ganglion head rest is arranged to prevent the head from wobbling from side to side during operation. The head is held in the erect position and may be raised or lowered or turned from side to side by the use of the adjustable frame and universal joints. The base plate (Fig. 472 *a*) is secured to the swing leaf, *j*, of the Balfour operating table by a clamp, *i*. The swing leaf may be adjusted by the ratchet bar, *k*. The headpiece, *b*, has a spherical surface adjustment in the cup, *c*; it is secured in position by the thumb nut, *f*. The spring fingers, *g*, are adjustable and hold the patient's head in position. The upright, *d*, is hinged on *a* and supports *c*, which may be adjusted for height and angle positions through the rod, *e*; it is secured by fingers, *g*, to the headpiece, *b*. By adjusting the table, the swing leaf *j*, rod *e*, members *c* and *d*, swiveling piece *b*, and the fingers *g*, the surgeon may hold the head in any position desired.

## SCALPEL SHARPENING\*

G. G. LITTLE

It takes time and patience to acquire the ability to sharpen scalpels properly, and to give to every knife edge the same keen smooth sharpness. There is quite a trick in getting the right swing to the knife as it is being passed over the sharpening stone. Keeness is acquired by reducing the edge to a thinness limited only by the strength of metal required to keep it from breaking out or nicking too easily. Smooth-

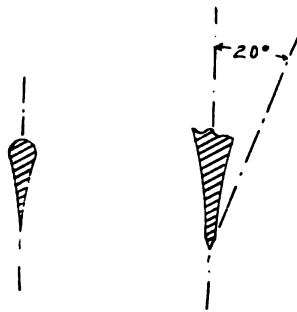


FIG. 473.—Cross section of a scalpel blade the sides of which are slightly concave. The surfaces come so close together that near the edge they are parallel and terminate in a cutting edge as shown at the right, enlarged.

ness is to be had only by the use of the finest abrasive stone known, and several important factors should be taken into consideration in selecting the stone for scalpel sharpening.

There are two kinds of abrasive stones that are the most adaptable to scalpel sharpening. They are composed of an even grain or hard crystalline structure that gives the desired cutting edge to the knife blade and retains a smooth true surface much longer than any other stone. Such properties are all very important when the stones are in constant daily use.

The first stone is known as the Pike India oil stone and is used for quickly reducing the cutting edge to the required thinness preparatory to giving it the smooth cutting angle.

\* Reprinted from Surg. Gynec. and Obst., 1919, xxix, 81-83.

The second is known as the hard Arkansas oil stone which is a natural stone quarried near Hot Springs in the Ozark Mountains of Arkansas and is composed of millions of pure silica crystals, microscopic in size, of the greatest hardness and sharpness. So perfectly crystallized is this stone that it is nearly sixteen times more difficult to cut than marble, a feature of great importance, as it enables the hardest steel tools with fine points or blades to be sharpened without grooving the stone.

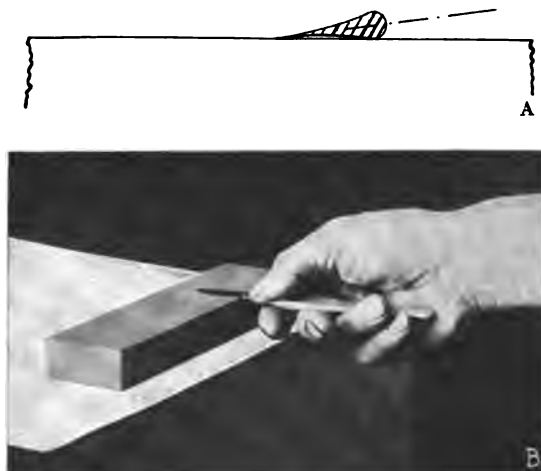


FIG. 474.—A. The position of the blade relative to the stationary stone when being reduced to the proper thinness. B. Passing the blade over the surface of the stationary stone to reduce the edge, the proper movement is to hold the blade down flat with just enough pressure to cause the stone to cut, move it lengthwise of the stone and near the end of the stroke raise the handle gradually, thus causing the curved side to come into contact with the stone and reduce the edge clear to the point. The movement is repeated in the opposite direction for the other side of the blade.

The Pike India oil stone is made of alundum which is a remarkable reproduction of the natural mineral corundum. Alundum is made by fusing bauxite, a soft earth resembling yellow clay and chemically the purest form of aluminum oxid, in the intense heat of the electric furnace. The advantage of alundum over every other known abrasive lies in its peculiar combination of hardness, sharpness, and temper. By temper is meant strength of grain and ability to wear under pressure. These stones, the Pike India oil stone and the hard Arkansas oil stone, are absolutely uniform in hardness and texture, most important qualities.

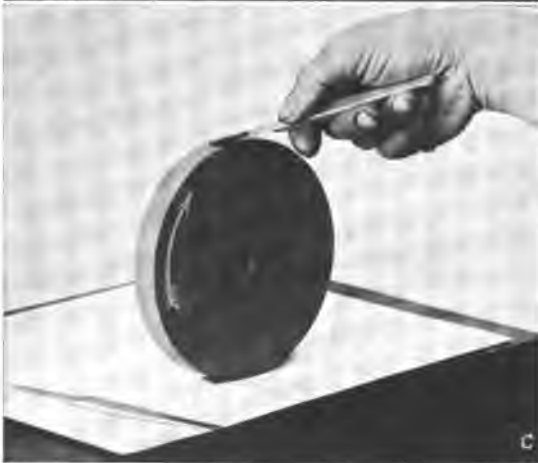
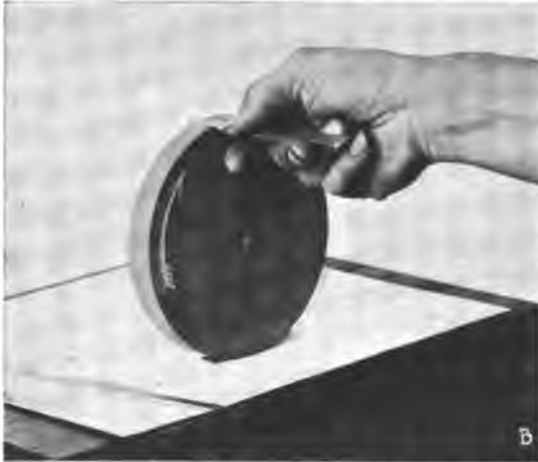
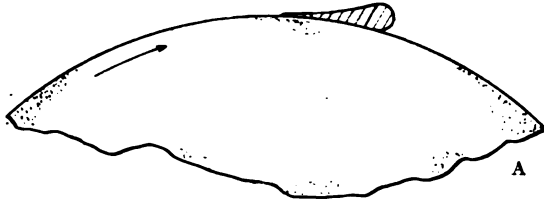


FIG. 475.—A. The position of the blade relative to the circular stone, the radius of which (3") controls the amount of concavity given to the blade while being reduced to the required thinness. B and C. The circular oil stone for reduction. The blade is placed on the face of the wheel and as the stone cuts away the metal the blade is drawn back and the handle gradually raised bringing the curved side onto the wheels and reducing the edge clear to the point.

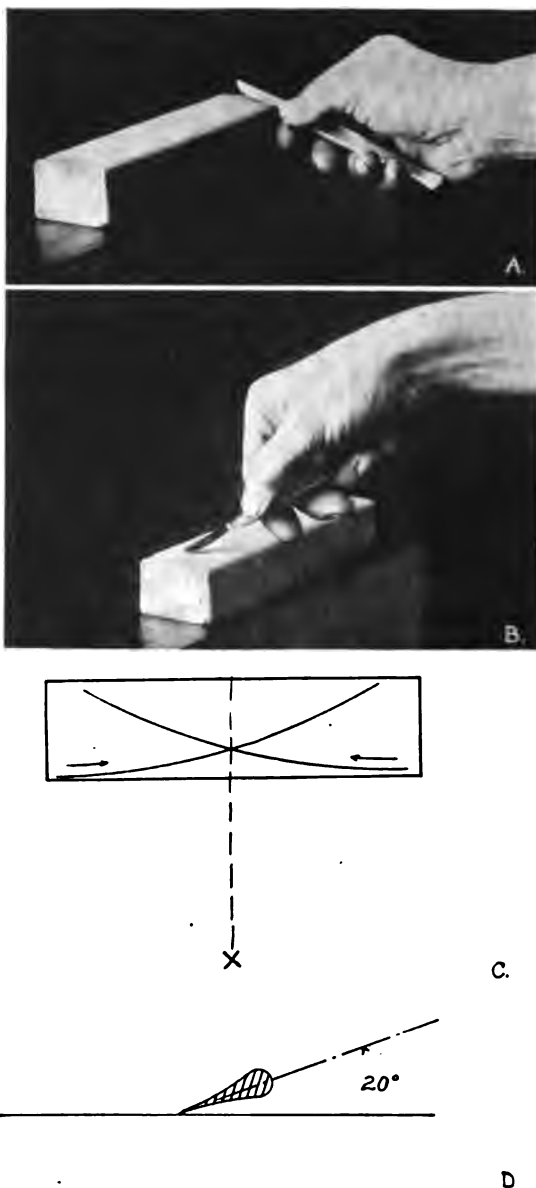


FIG. 476.—*A* and *B*. The position of the blade ready to pass over the hard Arkansas stone and to receive the final cutting edge, *A* being the starting point and *B* the end of the stroke. The handle has been raised to bring the whole cutting edge in contact with the stone as the blade passes over it. *C*. The top of the stone with two curved lines drawn on the surface which represent the path of the blade as it passes along. The movement is made as though to scrape the lines off and the entire edge is used. At the start of the movement the blade is held with the heel touching the rounded corner of the stone at the right-*A* and with the back of the blade raised about 20 degrees off the stone to give the proper angle to the cutting edge *D*.

There is a softer grade of the Arkansas stone that is more suitable for sharpening large knives that do not require the keen sharpness of the scalpel.

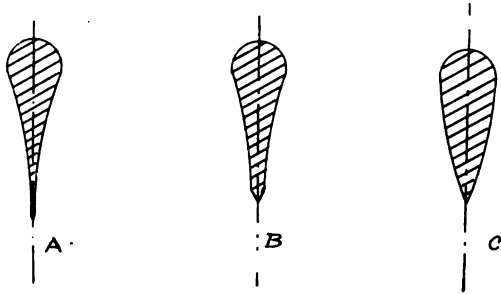


FIG. 477.—*A*, *B*, and *C*. Three blade sections. *A* is the outline of a perfectly shaped blade section that can be given a very keen sharp edge, while *B* is an outline of a blade section that has been sharpened without reducing the thickness so that it has become too thick to be made keen, though the cutting angle may be the same. *C* is an outline of a blade section that has been reduced on a flat stationary stone and shows that care was not taken to keep the sides straight; instead they were allowed to become rounded off toward the cutting edge, making it hard even to sharpen it.



*B*

FIG. 478.—*A*. Stone being rounded at the corners by rubbing it on a sheet of abrasive cloth on a flat surface. *B* shows the corners rounded to give a continuous surface for starting the stroke of the blade and to remove a possibility of nicks on which to catch the edge of the blade.

A light oil should be used to float the fine particles of steel away from the surface of the stone, thus keeping it cutting freely. We use gasoline because of cleanliness; oil, no matter how light, will leave

on the hands and on the work, a film that is more or less disagreeable.

When there is a large number of knives to be kept sharp it is advisable to install a motor-driven circular oil stone (Pike India stone of medium grade) for reducing the blades to the required thinness, as the work can be accomplished in less time than if the flat stationary stone is used.

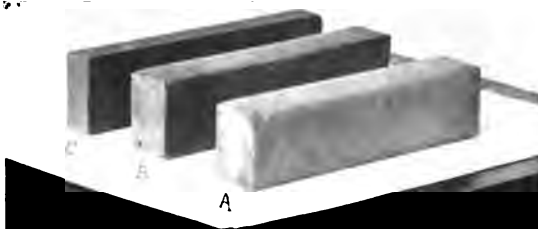


FIG. 479.—Three oil stones. *A* the hard Arkansas, *B* the soft Arkansas, and *C* the Pike India. The first two stones are  $1\frac{1}{2}$  by 2 by 8 inches and the Pike India is 1 by 2 by 8 inches; they are all standard size and can usually be bought of or through any hardware dealer who handles fine tools, or direct from the Pike Mfg. Co. of Pike, New Hampshire.

The first step in the process of scalpel sharpening is the examination of the cutting edge to determine its thickness, and to learn whether the edge is of the required thinness or whether it must be reduced before it is resharpened. Along the cutting edge will be seen a bright polished line on both sides of the blade. These lines are called “lands” and are caused by the action of the hard Arkansas stone as the blade is being given the final cutting edge. After the blade has been properly



FIG. 480.—Calf skin leather (soft finish) is folded once for testing keenness. The edge of the knife is carefully touched to the rounded surface with a slight draw movement which will cause it to cut the leather.

reduced to the required thinness it may be resharpened about four times before it is reduced again, though it is advisable to give it a few strokes on the Pike India oil stone (the stationary one) and then give it the final cutting edge on the hard Arkansas stone. Note that the edge of the blade is always forward when sharpening so that the wire edge is worked off instead of being put on.

The proper position of the operator while sharpening a scalpel is to the left of the stone so that the elbow is at a level with the surface and on a line with the center.

## A METHOD FOR PRESERVING A SHARP SCALPEL IN EXPERIMENTAL SURGERY\*

F. C. MANN

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One of the problems in the mechanics of surgery is to maintain instruments in good working condition. In experimental surgery it has been found difficult to keep a good edge on scalpels, mainly due to the fact that section of the animal's skin dulls the edge of the knife. This problem is solved by obtaining a cheap knife to make all skin incisions. A high grade, all metal, small paring knife has been found to suit our purpose. These knives are made in various shapes so that almost any style can be obtained. They sharpen readily and are quite strong. As they are composed entirely of metal they withstand boiling. They usually can be used three or four times before they need to be retouched on the stone.

The present technic for making an incision is as follows: After the usual preparation, the skin and fascia are cut with one stroke of the paring knife which we term the "skin knife." The sharp, heavy blade of the knife makes a sure, clean incision possible. As soon as the skin incision is made, the knife is dropped in the pan for used instruments and after catching the bleeding points and placing the skin towels in position the rest of the incision is made with the regular scalpel. While the knife was obtained for the purpose of saving the edges of the scalpels, it also makes possible another point of technic which some surgeons hold important, namely, the use of a scalpel which has not passed through the skin for the deep part of the incision.

\* Reprinted from Jour. Lab. and Clin. Med., 1919, iv, 578.



## TURKISH WASH CLOTHS FOR PACKS IN EXPERIMENTAL SURGERY\*

F. C. MANN

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Many different materials have been used for packs. Chief of these is gauze, and for general use it is doubtful whether any material can be found to replace it. In our own work in experimental surgery, however, we have found that the turkish wash cloth is more satisfactory. These wash cloths have several advantages over other materials which we have used, gauze, rubber, silk, and paper. They can be secured easily; various sizes can be obtained; when placed in position they remain in place; and contrary to our preconceived idea, when moist they do not irritate delicate surfaces such as the peritoneum or pleura, nor does any of their rough surface come off into the wound. During more than a year's use they have proved very satisfactory, and they are much cheaper than the other materials.

\* Reprinted from Jour. Lab. and Clin. Med., 1919, iv, 639.

## THE USE OF TURPENTINE RESIN IN TURPENTINE AS A FOAM BREAKER

E. C. KENDALL

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Many substances have been suggested for breaking the foam which is formed by the rapid aeration of blood and other fluids. Among the best of these agents are caprylic and amyl alcohol. If only an occasional determination is made, caprylic alcohol or amyl alcohol is entirely satisfactory and the cost is negligible, but if a large amount of work is carried on for a long time the cost of material becomes of importance.

During the past year attempts have been made in our laboratory to find a cheaper substitute for amyl alcohol. Among other substitutes, turpentine was found to have distinct foam-breaking properties. As the sample tried was not quite neutral it was decided to distill it and it was then found that the distilled turpentine had lost practically all its foam-breaking properties. The real foam-breaking agent appeared to be some impurity which was contained in crude turpentine and which could be removed by distillation. The most probable impurity was resin, and we found that on adding resin to turpentine its foam-breaking power was greater than that of amyl alcohol. We now use from 1 to 2 c.c. of a 20 per cent solution of resin dissolved in turpentine. This is made by breaking the resin into small pieces and dissolving it in the turpentine on a hot-water bath. During the last six months we have encountered no blood which could not be aerated at the most rapid rate with this foam-breaking agent. If the solution of resin in turpentine is not neutral to alizarin, either 0.1 normal sodium hydroxid or sulfuric acid is added until the solution is exactly neutral. Resin dissolved in turpentine is an efficient foam-breaker, is very easily prepared, and is much cheaper than caprylic or amyl alcohol.

\* Reprinted from Jour. Biol. Chem., 1919, xxxviii, 529.

## THE USE OF COAL AS A SUBSTITUTE FOR TALCUM TO INDUCE RAPID BOILING\*

E. C. KENDALL

While we were attempting to improve the method for the determination of small amounts of iodine, some substitute for talcum was sought which would cause a rapid boiling of the solution. The usual laboratory agents, such as pumice stone, powdered brick, broken glass, glass beads, and granite, were tried and found to be unsuitable. The theoretically ideal agent would have to be insoluble in acid and alkali and not acted on by reduction or oxidation.

Carbon in its various forms answers the theoretic requirements. It was found, however, that the various forms of carbon differ greatly in their power to cause rapid boiling of a solution. While powdered charcoal or coke has slight power in this respect, anthracite coal is without exception the very best substance to bring about the rapid boiling of a solution. The formation of bubbles does not take place on the sharp edges and corners alone, but over the hard, smooth surface of the coal minute bubbles form with great rapidity, and under some conditions a piece of coal 2 cm. cube can be raised from the bottom of the flask by the rapid formation of bubbles on its surface. It acts in a similar manner in the acidification of a carbonate or sulfite solution. The bubbles of sulfur or carbon dioxide are liberated on the surface of the coal. Coal is equally successful in preventing bumping in Kjeldahl flasks and in the distillation of organic liquids. If the coal is kept under water indefinitely it becomes less active, but heating in an oven will restore its activity. Another great advantage of coal is the fact that it is easily cut with a dental drill and a small glass hook can be inserted in the coal. After the solution has been boiled, if it is so desired, the coal may be removed by a glass rod with a hooked end which passes through the glass hook in the coal. One or two pieces about 1 cm. cube are better than many smaller pieces. As powdered anthracite coal has almost no effect, the specific and unusual properties of hard coal in this regard must be due to its structure.

Reprinted from Jour. Am. Chem. Soc., 919, xli, 1189-1190.

## **GENERAL**



## SOCIALIZATION OF MEDICINE AND OF LAW\*

W. J. MAYO

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The physician of the old school, with his top hat and double-breasted frock coat, who practiced as an individual in all branches of medicine and surgery, has practically disappeared. He has given place to a new type of physician, who, discarding the stage scenery of the old school, dresses in the sack suit of the business man and works, not as an individual, but as a part of an organization in which the state in one way or another, has become his partner and aids him in his work. This change in the outward appearance of the physician is one of the visible results of the public's recognition of his sound scientific training and the part that modern medicine plays in the health of the people, as shown by the present-day methods of dealing with the great pandemics such as cholera and the plague. Even more impressive are the triumphs of the physician over the more common diseases, such as typhoid, a disease which man had come to look on as a visitation of providence, and which has killed more persons than the unfamiliar and therefore more terrifying diseases of ancient civilization.

### PREVENTIVE MEDICINE

Civilization and intellectual growth depend largely on preventive medicine. If each person were left to develop his own resistance and immunity, we might expect eventually to reach the condition of China where all effort is intuitively expended to protect the body against disease at the expense of intellectual advancement. The Chinaman, with his ancient civilization, slowly developed individual resistance to bad hygienic conditions. His resistance to the common diseases, his acquired immunity to many, and his ability to extract nourishment from ill-suited foods, not his dulled intellect, have made him a formidable competitor of the American laboring man and have caused his exclusion from our country.

\* Presented before the joint meeting of the Wisconsin and Minnesota State Bar Associations, La Crosse, Wisconsin, July, 1919.

The American Indian was nomadic without knowing why. By moving constantly from place to place he escaped the consequences of his filthy ways. Many of his descendants, living the life of the white man, died from filth-diseases. The length of life of the Indian was in direct proportion to his hygiene after he adopted a fixed abode.

One of the chief differences between the animal and vegetable kingdoms is their relation to their own excreta. The fallen leaves of a plant act as its mulch to increase growth; the excreta of animals are poisonous to them until they are given new organic life through plant action. In general, disease-producing microorganisms may be pictorially divided into three classes:

1. The obligates, that must subsist on living animals, of which those causing syphilis, malaria, and tuberculosis are familiar examples. These obligates do not always destroy their host as by so doing they would become extinct through lack of nourishment.

2. The saprophytes, that live only on dead material and are responsible for diseases only as they produce toxic chemical substances which directly or indirectly lead to disease.

3. The facultative bacteria, that subsist either on the living or on the dead substances. From such dual functioned microorganisms come the great pandemics such as cholera and the bubonic plague. These diseases are deadly because the microorganisms causing them are able to destroy their host without imperiling their food supply. The Chinaman, because of his failure to accept even the most ordinary health measures in the prevention of disease caused by facultative bacteria, makes his country the continuous home of the various plagues which at intervals escape into other lands, endangering all mankind.

#### PUBLIC HEALTH

We pride ourselves on our advancing civilization and intellectual superiority. If we are to continue to advance, the public health service must be made the first function of the state. It is probable that neither prohibition propaganda nor an appeal to the conscience of man has caused the rapid advance of the temperance movement, but that pure water has made this possible. It is assumed that the drinking of spirituous and fermented liquors is due to an evil inborn longing, to be stamped out only by the exercise of individual self control. Is this true? In France and Italy the drinking of billions of gallons of wine saved the people from extinction; they could not

have lived had they drunk their polluted water. The Teutonic countries turned to beer to secure a sterile drink; England had ale and wine, and temperance countries, such as Turkey, had tea and coffee. Simultaneously with Vienna's introduction of a pure water supply from the mountains, her per capita consumption of spirituous and fermented liquor was reduced 40 per cent. The introduction of a pure water supply in the various states in our own country has been followed by a temperance movement, and finally by prohibition. The drink habit is one of the many forms of individual protection resorted to by nature to save man from filth diseases which cause death, or that which is worse than death, intellectual deterioration.

Medicine in the great war was triumphant. For the first time in the history of wars, the number of deaths from casualties was greater than the number of deaths from disease. Eighty-five and five-tenths per cent (Billings) of the injured soldiers were able to return to the fighting line, and 5 per cent more were made fit for special or limited military duty in areas in the rear; in the Civil war nearly half the soldiers were out of the war permanently after injury, and a high percentage were at all times too ill from disease to render efficient service in battle. In the Spanish-American war one man died of gunshot wounds to thirty who died of disease (Smart). Typhoid, the great enemy of both army and civil life, has been eliminated by a pure water supply. If this cannot be obtained normally the water is rendered safe by treatment with hyperchlorates, and the soldiers are protected against accidental infection by antityphoid vaccination.

The public has been almost unconscious of the growth of preventive medicine and public hygiene, and but little has been accomplished along these lines in comparison with all that may be done. Smallpox can be wiped from the earth; this has been done in Germany. The continuation of the disease in any country is a disgrace; it is due to the ignorance and prejudice of some, and the indifference and selfishness of others. The examination of school children and the giving of instruction with regard to teeth, tonsils, and so forth, is of primary importance in guarding against infections. Infections are responsible for metabolic changes which later result in disease of the nervous system, of the heart and kidneys in middle age. Yet, even with the ineffectual health measures that have been instituted, marvelous good has been accomplished. In the last century the average life of man has been increased fifteen years (Vaughan); as much more could be



added in the next twenty years if the facts now in our possession were effectively employed.

Of all coöperative enterprises public health is the most important and gives the greatest returns. To obtain necessary legislation we must depend on the education of the public, and this, I am glad to say, is rapidly progressing. That there is much opposition to legislation for public health measures and that such opposition is always from the same group of obstructionists whose prejudices are believed by them to be principles and to whom controverting facts have no meaning, is well known. But such opposition is not entirely harmful. The agitators at least attract an audience before whom the truth may be placed. People as a whole are more interested in their individual affairs than in movements to enforce public health measures, and unless sickness actually exists in their own families, or unless they are in the midst of a strange epidemic, they pay very little attention to such matters.

#### THE PHYSICIAN AS AN INDIVIDUAL

Individually, no man is respected more highly than the physician. Collectively, doctors are often looked on as a nuisance because, in season and out of season, they try to advance public health measures to reduce sickness and, obviously, to reduce the number of their patients. Such unusual acts of philanthropy are very apt to be viewed with suspicion by the general public and particularly by legislators who fail to understand why a man should destroy his means of earning a livelihood. Moreover, the public does not wish to be disturbed, or to be forced in the midst of health to dwell on the unpleasantness of sickness, much as the man who is irritated by being awakened in the night by a disturbance in the street at the time cares little what the cause may be even if he is eventually to be benefited. Thus it is that the medical man in his efforts to secure health measures for the prevention of disease is not only treated with indifference but also often is vigorously opposed by the public and by legislators. The public may always be generously enlisted to remedy existing evil; to prevent some future evil is less appealing.

The surgeon is brought constantly in contact with persons suffering from diseases for which the knife is the best remedy. He is rewarded by the gratitude of his patients; and yet very often he furnishes a remedy for diseases that are unnecessary and preventable. On the

other hand, the public health officer and the sanitarian, who save thousands of lives by preventive measures, are looked on as disturbers of the public peace. The practice of preventive medicine calls for a man of the highest order, one who is endowed with the spirit of the crusader, and who is satisfied to do his duty without thought of reward.

#### HEALTH INSURANCE

In the last generation the whole trend of thought has been individualistic. Remedies are sought for deplorable conditions with little investigation of the underlying causes, and too often monetary considerations lead to action. An enormous number of undigested laws are passed at each session of a legislature and each law is supposed to be a dose of medicine for a particular evil. Some of the laws are necessary, others are unnecessary or harmful. Many of these are for the purpose of quieting popular clamor and not for enforcement. It is just such legislative follies and failures that lead to the prevalent disrespect for the law and make it so difficult for medical men to secure legislation for public health service. The public is badly advised, voiceless, and often powerless against the opposition of individual interests which would be adversely affected by the measures advocated. At times it actually appears that those who profit by the physical and social diseases of man have a vested right in the continuation of the evil conditions which produce them. Now that potable water has been largely secured, at least in cities, polluted milk and unsound foods that are sources of disease should have such legislative attention as will give increased strength to the pure food laws. This era of law making, a little remedy for each little ill, however, is showing signs of evolution in the form of class legislation, such as the Workmen's Compensation and Health Insurance, a groping in the dark from the individualistic to the general in public health measures. Health insurance is sound doctrine if wisely administered, but unfortunately it is not based on the idea of keeping the workmen in health, but rather on caring for him when he is sick. In no way are the workmen as a group better protected from disease. Their medical attention is quite as competent or incompetent, perhaps a little cheaper than before. Little attempt is made to organize or to improve medical service. The workman pays a certain definite amount for the year and is taken care of if he is sick. Sometimes a competent doctor is

employed to do the work, but too often one who has been unsuccessful elsewhere and can be secured cheaply is employed.

Health insurance and its effect on workmen have been well illustrated in Germany. It was at first believed in Germany that such health legislation would reduce the percentage of sickness, for example tuberculosis, and that the death rate would be lowered because of earlier treatment. But the prevalence of and deaths from tuberculosis were not reduced. A fraction of the money spent would have protected not only the workmen, but also the entire population. This again demonstrates the futility of attempting to protect the individual, whether workman or not, from contagious and infectious diseases. The individual is an integral part of society and is endangered by the contagious diseases of any other individual; if he would be well himself he must see that his community as a whole keeps well.

The workman's compensation in some ways has been an economic loss. The workman with a felon on his finger, for instance, was entitled to the benefits of full time disability and remained inactive for two months, whereas, under ordinary circumstances, one week would have been the maximum full time, with a gradually increasing industrial output for the remainder of the period. This form of insurance also fostered malingering, and consequent industrial loss. Malingering finally became a public scandal in Germany. In England, too, health insurance measures have been badly carried out. The people who were supposed to be benefited were those to whom the state had already furnished more or less medical aid; under the health insurance act the same doctors cared for them exactly in the same way, and malingering in England also became prevalent. We should have health insurance for the workman who is ill, but such service should be adequately performed, wisely supervised, and should come from organized group medicine. The patient should have access to trained specialists so that all phases of injuries and diseases may have skilled attention instead of being cared for by the general practitioner who, obviously, has little knowledge of the specialties.

#### GROUP MEDICINE

The medical profession is grouping itself along scientific lines, not for the profit of the doctor, but in order that he may more adequately and satisfactorily perform his work. This will give patients the benefit of modern medical knowledge. It is not to be inferred that

there will be no individual practice, or that all medicine will be practiced in groups. On the contrary, the state health departments are furnishing, through their laboratories, the diagnostic aid which gives the average practitioner expert reports on pathologic and bacteriologic specimens and enables him to apply in the care of his patients the data which he personally has neither the time nor the training to develop. The state also furnishes, free of charge, diphtheria antitoxins, vaccine for smallpox, typhoid, and so forth. This important work of the state should be extended. Certainly 50 per cent of all sickness is preventable, and it is the duty of the state to guard the health of its citizens through the prevention of disease. The people should be made to understand that the state is culpable if its citizens are allowed to become ill through manifest neglect. It is probable that such an understanding by the people would result in greater good through new legislation than all the work and all the sacrifices of the medical profession which have secured the present laws.

#### INDUSTRIAL EFFICIENCY AND PROLONGATION OF LIFE

In the past, industry was so prodigal of its human machinery that no precaution was taken for the protection of the life and the limbs of employees. Immigration furnished an enormous supply of raw material and vacancies were filled. Today this supply is no longer so freely available and industry is caring for its workmen most assiduously. It is recognized as never before that men who are trained for a certain work are an asset, and that with care their lives may be prolonged. In the past it was difficult for a man more than 40 to get a job, if more than 50 it was practically impossible. The older men are now regarded as the most valuable, they are trained for the work, their habits are steady, and their views less inflammable, thus discouraging industrial disturbances. As a result of new conditions some industries have developed fine economic organizations that serve as examples of what may be done. Given legislation and proper control, the average life of man may be lengthened at least ten years, and his industrial efficiency will be prolonged in proportion.

The new appeal is for a partnership between capital and labor in industry, and such partnership must come. The bull-headed employer and the unbalanced labor agitator must be controlled. It has been said that corporations do not have souls, only dividends. It is no wonder that laboring men form unions for self protection, but unfor-

Unfortunately many labor organizations when in power demand privileges of the same general character that they had united to overthrow. Successful partnership demands mutual confidence and honest striving for the object in view. The basic fabric of a partnership between capital and labor is a contented industrial community of healthy, well housed, properly clothed, and properly fed people, who possess at least some of the advantages every intelligent citizen desires for himself and his family. But the laboring man must mend his ways if he is to enlist the aid of capital and retain the sympathy of a public of which he is a part, not the whole. If a man puts forth his best efforts forty-four hours a week he is economically more satisfactory than if he works inefficiently sixty hours a week. Such a schedule gives the workman time for the enjoyment of his constitutional rights, life, liberty, and the pursuit of happiness, and under it he becomes a member of the privileged class of the nation. If he limits his output and insists on regulations which cause expensive equipment to lie idle, however, he is not loyal to the organization by which he is employed, and he cannot be received into partnership.

#### CONCLUSIONS

Sanitarians trained in industrial community work are needed. Fortunately, schools for the training of such men are now being established. A department of Industrial Medicine and Public Health in the University of Cincinnati and a department of Industrial Hygiene at Harvard are now in operation. It is the part of wisdom for both capital and labor to train men to prevent accidents and disease and to furnish adequate, not cheap, care for injured employees which will restore them to economic usefulness, rather than to pay out money in compensation and lose the output of the injured or sick man.

Our state and county institutions exercise custodial care of their inmates, giving little attention to the fact that many of them are capable of restoration to a degree of efficiency which would make them self supporting instead of life-long charges of the state.

If America is to succeed in maintaining her position in international commerce and to continue to pay the laboring man wages proportionate with the American scale of living, it must be done by rendering the American laboring man more efficient and longer lived, that he may produce more. In this way only can we compete with the nations of the old world, where the laboring man lives on a lower wage

scale, is short-lived, and consequently less efficient, and less an asset industrially. America has been wasteful of her timber and other great natural resources, but the greatest waste of all has been that of health and human life. If we are to continue as leaders of the world's civilization, we must have legislation that will provide money and power to prevent and control disease, money to place force behind the pure food laws, and laws that will remove public health service from local politics, which is the bane of all state and municipal civic functions. The legal profession furnishes the trained intelligence which guides legislation, and must assume the responsibility.

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## PRESIDENTIAL ADDRESS\*

W. J. MAYO

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The American College of Surgeons is beginning its seventh year under most inspiring circumstances. More than three-fourths of the Fellows of the Association have been in their country's service and have returned to their work with renewed vigor and enthusiasm. In spite of the war years, the College has made progress along all lines. The Clinical Congress of Surgeons of North America has been taken over by the American College of Surgeons. In the future the educational, scientific, and moral standards of the American College of Surgeons will be maintained, and only its members and invited guests will be welcomed to the clinical meetings.

Standardization of hospitals has made great progress under the able leadership of the Director of Education, Dr. John G. Bowman. As the result of the efforts of the College, the great majority of hospitals in America of more than 100 beds will institute the restricted staff, and install the laboratory facilities and record systems which the American College of Surgeons believes to be essential.

It is the desire of the Founders of the American College of Surgeons that the association shall be democratic, and that its membership shall be open to all those men of sterling character, ability, and training in general surgery, and in the various surgical specialties, who are within the limits of North America. For, when all is said and done, the College stands for service to all the people, and unless a sufficient number of men of high ideals and professional qualifications is eventually secured, the organization will have failed to live up to its great opportunities.

The exact number of men required to perform the duties of caring for the various serious surgical ills of the 115,000,000 people of North America is at this time a matter of speculation and, so far as I know,

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there are no data on which such a computation can be based. However, an estimated number might be fixed to serve as a target for criticism, of at least one surgeon to 10,000 persons. This percentage is about the same as that furnished to England by the Royal College of Surgeons of London. That there will be, in the next decade, such a number of eligible men, I am confident. Objection has been raised to an association of so large a membership. It is maintained that this would mean a lowering of educational standards. If the principle is established that the association first of all is for the benefit of the people, I believe a working arrangement can be made which will, in a tentative way, meet the requirements. The next generation will not be so greatly troubled as the present one by questions of educational standards. The medical standards of the whole country have been raised to a point not exceeded by those of any other country. In the present generation, by reason of divergent standards, there will have to be a certain amount of latitude to meet the existing conditions.

Knowledge obtained by observation, experience, and from the printed page is possessed by many men. When knowledge is translated into proper action we speak of it as wisdom. Many men have great wisdom, in their knowledge of useful things, yet may have but a limited book learning. Personally, I believe that the wise honest man who can bring a high order of skill to bear on surgical infirmities should not, at least in this generation, be refused admission to the College because of a lack of fundamental training.

In the adoption of standards or requirements for admission into the American College of Surgeons, character should be first considered. The dishonest, conscienceless man who has surgical skill is most dangerous in any community. Unnecessary operations, even when performed with a high order of technical ability, are the bane of present-day surgery, but, owing largely to the American College of Surgeons, such practices are markedly on the wane. However lenient we may be in estimating the value of the older and disappearing generation of surgeons, our standards for the younger and coming generation of surgeons, who have had and who will have had opportunities to acquire learning, should be high and increasingly high as future standards and educational requirements are raised.

In the future, the American College of Surgeons will not only demand that the candidate shall be a graduate of a reputable medical school and have had hospital experience and be licensed to practice,



but also that he shall have had special training in the particular surgical specialty which he intends to practice. In making these requirements it is the duty of the College to see that facilities for obtaining the special training are developed. Three years at least will be required for such special training. At the present time the man who possesses the B. S. and M. D. degrees and has had one year of hospital training averages twenty-seven to twenty-eight years of age. Add three years to this training and he is 30 to 31. Will this secure the best results or will the man reach his life work at too late an age? We must also consider that during the entire period of his education he is not self supporting. Will not this have a tendency to make the surgeon a member of an aristocracy to the ranks of which the sons of rich men will be the only ones who will have easy entrance? Investigation was made of the professional standing of the graduates of the medical department of the University of Michigan fifteen years after graduation. It was shown that those who graduated before their twenty-fifth year had made, on the average, greater scientific progress and were a greater asset to their community than those who graduated after the twenty-fifth year.

I think we are all agreed that the actual time spent in the professional part of this education should not be shortened. I think we are also agreed that one of the faults of the educational system of our country is a loss of time and effectiveness in the preliminary educational methods. The university has been made the base of our educational system and it should be the apex. Only a small percentage of those who enter our public schools ever reach the university, yet the university greatly influences the educational policy even in the grade schools. I am convinced that at present two years of time are lost in the grade schools, and that the education given is not altogether the most desirable for the making of American citizens. A six-year course of grammar school education, divested of any university significance, should be a strict government requirement in all schools, private as well as public, and given in the American language. It should be the purpose to give a common education in the common things that are to make us a united people, and such an education might well be made a requisite for the exercise of suffrage.

The high school could be reduced to three years instead of four, and in it for the first time should the university be considered. Languages should be optional in the high school, but I believe that Latin and

modern languages are of great value to the professional man. The high school now recognizes the material facts of life, and gives an education in mechanics and agriculture, business, and the industries, as well as the traditional cultural education, and these courses should be further extended.

It is sometimes difficult to follow the academic mind. The more or less cloistered life that is led by many college professors has given traditional cultural education too great an influence. Modern educators today do not believe that teaching in one subject as, for instance, mathematics, has greater power of mental training than other subjects. The old time educator would consider this rank heresy. His mind still clings to the view that any education which might be used commercially is not cultural, a view which is wholly undemocratic and based on an out-worn caste system.

In no place has this traditional view of education been more pronounced than in the universities. It has been only within recent years that the university faculties would accept the view that the anatomy and physiology of man have cultural training value, although they were convinced that the anatomy and physiology of plants have such value. There has been a slowness of universities to give credits for any kind of work which might be used for gaining a livelihood, even so holy a cause as caring for the sick. And today less credit is given in these subjects than for others which have no more training value. Do not understand me as desiring to lower the standards of universities in relation to cultural education. Far from it; but I do object to the present attitude which desires to force every type of education into the one mold. The great problem now is to obtain the money to give an education to all those who desire it. The purpose of the university is to give an education not to the few but to the many, and it should be emphasized that the giving of degrees is only incidental to this purpose. Every unnecessary step, every unnecessary regulation which delays or obstructs the progress of a student prevents someone else from obtaining an education. The academic answer is: Raise standards until the number of those who can—not desire, but can—obtain an education is reduced to the number who can be given the present form of education. Our country depends not on a cultured class alone, but on the average intelligence, and in the last analysis on the number who will be able to obtain an opportunity to get an education. It should be the duty of the Fellows of the

American College of Surgeons to see that certain existing conditions be remedied so that the medical schools may graduate their students at an earlier age.

In this connection, I quote from the 1918 report\* of C. G. Schultz, Superintendent of Education of the State of Minnesota, now of the Government Department of Education, Washington:

"It requires a total school enrollment of approximately four hundred fifty to produce one college graduate. No one questions that it is desirable that this one graduate should be produced. But that a large part of the energies of a school community should be devoted to this end seems lacking in sound business sense. Surely such a procedure in no way contributes to the fulfillment of our democratic ideal of the open door to equal opportunity. In order that we may prepare one pupil for college we cannot justify the neglect of those forms of training distinctly desirable for the four hundred forty-nine who must follow pursuits other than those open to the college graduate. The same reasoning leads to the conclusion that we cannot justify our insistence upon the maintenance of high schools for the sole purpose of training all pupils to go to college when only one out of ten goes and only one out of thirty graduates."

The expense of our educational system is a serious burden on our taxation resources. By efficient methods a much greater percentage of our young people might secure higher education without an increase of the present burden. The average child should not be entered in the common school under the age of 7, but should be taught in the kindergarten, given six years in the grade schools, and three in the high school. At 16 the student who desires it is ready for university training. The freshman and sophomore years, under university supervision, may be given in the home high school under home influences. At the more mature age of 17 to 18 the students leave for the junior and senior years in the university. Such a program contemplates cutting only three years from the grade and high schools, does not increase the cost, and doubles the capacity of the university for the giving of advanced education. This is not purely theoretic; such university high school courses are now given with university credits in some of the cities of Minnesota, among others Rochester, where C. H. Mayo, as one of the city school commissioners, has made the plan a success.

\* Twentieth Biennial Report, Department of Education, Minnesota, 1917-1918.

Another problem for which some wise solution must be found is the future management of the annual clinical meetings of the association. Even at the present time, with a limited membership, there are few cities in this country that can adequately care for the visitors at the meetings. It may be that a partial solution will be found in the development of clinical meetings to be held in various states or parts of the country in addition to the annual meeting for the convocation. It has also been suggested that the attendance at the annual meetings shall be limited to the members of the association, but, inasmuch as it is our intention to make the fellowship the first goal of the ambitious young surgeon after the completion of his training, it would seem that, so far as possible, promising young men should be admitted as invited guests.

In developing the sectional clinical meetings it should be borne in mind that the essential idea is educational—to develop better surgery. We must, however, remember that we, as a College, have a duty to perform to the public and to the profession, and this can best be brought about by close affiliation with the organizations representing medicine as a whole. We urge upon every Fellow that he become a member and a conscientious worker in his County and State Societies, and in the American Medical Association.

*Men who cannot become fellows because of lack of moral character should not be allowed to give demonstrations or hold clinics under the auspices of the College.*

Finally, I would call attention to the desirability of making the College of Surgeons truly American, by affiliation with the Universities of the sister republics in South America. The University of Lima, Peru, is the oldest university in America, and many of the South American universities have attained preëminence as educational institutions, with whom it would be of great benefit to be associated. I am sure a way will be found to consummate so desirable an alliance.

## EDUCATIONAL POSSIBILITIES OF THE NATIONAL MEDICAL MUSEUM

### In the Standardization of Medical Training\*

C. H. MAYO

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The crisis through which the world has just passed was reached at a mighty cost of money, suffering, sorrow, and life. It has freed the people of many nations; it is to be hoped that it has amalgamated the many peoples of our own; and if the world has been made safe, the tremendous effort will not have been made in vain. There will always be wars, but the waging of them will not be undertaken by the more highly civilized nations without just deliberation. The war has produced a mental quickening which has advanced our knowledge of the mechanical and the scientific far beyond that of a like period of peace. Our country is no longer isolated from other countries. Through science the world has become so contracted, as regards transportation, that whereas Columbus spent many weeks sailing from the old world to the new, it now takes but twenty-four hours to travel by air from the old world to the new, and but four and one-half days by water.

The medical profession may be justly proud of the record made by organized medicine during the war. The carrying on of this war, above all others, was dependent to an extraordinary degree on the physician. This statement applies to the medical profession as a whole, which is alike the world over, there being little difference in the capabilities of the leading men. In the wars of the past, generals have deplored the losses due to disease, which were always greater than from injury in action and were looked on as a necessary and inevitable accompaniment of war. In this war there were more than two deaths from injury and its results to one of disease, and yet the world lauded the strategy developed by commanding officers. There have been but few instances of military strategy and almost no cas-

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ualties among the higher officers in command. The real strategy of this war has been the control of disease by the men in the medical corps who reduced the loss of man power by preventive medicine, and by treatment controlled diseases that in the past were determining factors in the defeat of armies. The failure of the British in the Mesopotamia campaign was a medical failure due in part to lack of rank and attendant authority vested in the medical officers, and in part to army ethics, which made conferences difficult between officers of dissimilar rank. We need only to recall the yearly loss of 250 to each thousand men in the Crimean War, or the record of typhoid in the Boer and Spanish-American wars to realize the benefits of medical control of typhoid and of typhus fever when they started in Serbia. We must also recall the improved morale incident to the modern treatment and quick healing of wounds, whereby men were repeatedly returned to the ranks, instead of remaining permanently disabled and becoming a charge of their country, as in former warfare. Japan, one of the last countries to accept modern civilization, was the first to realize the importance of caring for the health of her troops; her medical officers were held responsible, and in consequence Japan was able to defeat an apparently stronger nation. The exceedingly low disease record of the Japanese army was reduced more than one-half in our training camps through the efficiency of that master of preventive medicine, Surgeon-General Gorgas, under whose direction the most efficient army medical organization was perfected that has ever been developed. The mortality rate of our troops in France was lower than that at home among civilians.

Long before our country became engaged in the struggle, hundreds of our profession, feeling the call of humanity, volunteered their services to France and England and served there faithfully and well, suffering many casualties. Our Reserve Medical Corps in France sustained 442 casualties; thus the percentage of losses of noncombatants equaled that of the infantry and artillery. Forty-six officers were killed in action, 22 died of wounds, 12 of accidents, 101 of disease, 4 were lost at sea, 7 were missing in action, 212 were wounded, and 38 were taken prisoners. For months before our country declared war, the first and best organization in preparation was the medical organization under the Medical Board of the Council of National Defense. These preparations were carried out for the purpose of aiding the Medical Department should war be declared. Practically one-third of

the active members of our profession, whose age, training, and capabilities met the requirements of the Surgeon-General, were commissioned for service. Seventy thousand of the medical men not enrolled in the Medical Corps in active service were members of the Volunteer Medical Service Corps. In this group were included the members of the 5000 local examining draft boards.

It is deplorable, and a blot in the history of this war, that the work of the American medical profession was not recognized by the general staff and that rank, according to responsibility, was withheld in most instances until the war was nearly or quite over. A comparatively long period of service in Washington enables me positively to state that the same unfairness toward the medical army officer still exists. Our government has maintained, at great expense, special places for the training of its army officers, even for their preliminary education, such as West Point for the Army, and Annapolis for the Navy. Students are given opportunity for service after graduation by continued training, maintaining the highest efficiency possible. The government in the past, however, has been at no expense in the training of the medical officers, but it has a postgraduate school for the purpose of training in the theory and practice of military medicine. No account has been taken of the fact that the men in the Medical Reserve Corps had had an average training of at least twenty years, and that their university course, and medical courses had cost not less than \$5000 for each person. In spite of the injustice of rank and the inaccuracies of assignments, the members of the Reserve Medical Corps sacrificed freely and willingly that our troops might receive the best that medical education afforded. The work in hospitals, including general and special practices, should at least qualify the physician to be placed on a par with the line officer of the army who has had a similar number of years of inactive duty in times of peace. The soldier is rewarded or promoted for risk of life and personal valor; an officer who is given authority to command the destruction of life may have spent but a few months in a training camp, while the medical officer who is responsible for the preservation of life devotes many years to preparation. I believe that the necessity of higher rank is essential only as it represents authority and responsibility, and it is required by the civilian medical officer during his period of service. I feel sure that should military service again be required, those in authority will be compelled to give adequate recognition to the medical officers as a vital point of justice.

One last point and I am through with suggestions for the reorganization of army rules which have been well arranged to give a multitude of official positions in time of peace but are most cumbersome and fruitful of delay in time of war. If there must be a general staff, instead of assistant secretaries over divisions, it is highly important that the Surgeon-General's Office should have a representative in each division as a liaison officer.

Surgeon-General Ireland is a most worthy and capable commanding officer for the medical department; he had under his charge a volunteer service of enlisted men, nurses, sanitary corps, dentists, and medical officers numbering 300,000; with the transference of the wounded and diseased, he had from 500,000 to 800,000. It is well to call attention to the small number of superior officers assisting the Surgeon-General as compared with the number maintained for corresponding thousands of able bodied men in the regular army.

The general training, discipline, and broad education of the youth who participated in the war should insure a just and sane political management of our country for two generations. It is apparent from the rules of the organization of the veterans of this war that they have banded together for the purpose of giving to our country rather than taking from it. The protection against disease and the care of health during the training for war and during war will be recognized and demanded by them as their right, and the right of posterity in time of peace in order that in the future 36 per cent of youth in the third decade of life will not be found incapacitated by disease and its results, should they be called to defend their country. The records of our draft boards, now made public, show a startling lack of interest on the part of our national, state, and local authorities in their responsibility fully, and often even partially, to protect the people against preventable diseases and the accidents of industry. It is a poor government that does not realize that the prolonged life, health, and happiness of its people are its greatest asset. The sum of money appropriated by the nation to expend for the prevention of diseases in man is, indeed, meager compared with the appropriations for the prevention of diseases in animals, and for the development of agriculture. Congress dare not investigate labor conditions for the purpose of maintaining a rational control of labor hours, and to control the value of labor in proportion to the investment. It is conceded, of course, that the manufacturers must be encouraged, and that small business operations only must be controlled by congressional act.



Because of the high cost and rapid turnover of labor, manufacturers, however, are recognizing as a necessity the protection of the industrial workers. The newer methods of treating injury, as developed by the war, will prove of the utmost advantage in caring for the accidents of industry. But many hundred cases of trachoma, and thousands of cases of hookworm, in fact, all forms of disease that can be prevented, controlled, or cured, still exist. The serums which have been used in the prevention of certain diseases, such as typhoid, typhus, and tetanus, have now become commercialized, and their widespread use certainly places them beyond the criticism of the ignorant. Colonel Russell of the Regular Medical Corps deserves great credit for being the first to free the army of any nation from typhoid.

The laws of civilization signify progress and efficiency along scientific lines. Such progress and efficiency are due to the initiative of comparatively few persons who serve as a stimulus both to the professional and to the lay public. Public demand is the only true stimulus for tradesmen and professional men alike. This can be advanced only when the nation adopts the slogan, "Educate the public."

The standards of the medical profession have been raised from time to time, and great strides are being made to further the progress, wholly through the efforts of its members. Hospitals are being standardized, surgery is being standardized, and everywhere the subject of sanitation and hygiene, dentistry, school inspection, and child welfare work is receiving more attention than ever before. From the lessons learned through the war we may now hope to have government standards of all scientific progress. There is no national control of education to develop Americanism. It has been shown that eight and one-half millions of our people of more than ten years of age are uneducated, and 70,000 of our young soldiers could not read nor write. This is not startling, as we are habituated to ignorance; but to have this secret become known to the world is humiliating to those devoted to foreign missions, and will surely be the basis for the appointment of a cabinet officer of education, who will undoubtedly deal with the medical aspect of health problems of education by instituting another medical board in Washington to overlap the functions of a dozen similar powerless boards. Human life and health have been so cheap that it did not seem necessary to safeguard them until we learned how many of our youth in the third decade were physically incapacitated for army service. Through the psychology of war and by co-

ordination of effort may it not be possible to better many conditions with regard to health problems? We must secure a certain degree of health; state or socialized medicine by which to control its development is inevitable.

The government has dabbled in medical affairs at enormous expense for what has been accomplished. Every cabinet position, and many smaller boards, bureaus, and advisory committees in Washington, probably as many as eighteen, deal with certain phases of medicine. Thus under the Treasury Department is the Public Health Service; under the Agricultural Department, pure food and drugs; under the Department of Commerce, health statistics; under the Department of the Interior, the insane not otherwise cared for, amounting to a large number; under the Department of the Bureau of Labor, the accidents of industry, housing, sanitation, and child welfare, all under their various divisions, subboards, and committees, none of which will coördinate or give way. Their duties overlap and the expense is great. England is now establishing a ministry of health with supervision of all the educational problems relating to health, sanitation, and preventive medicine. Medicine has been tried and proved to a degree that will enable it to stand comparison with any other effectual work of our government. Why not, therefore, establish a cabinet officer of health, and unite, or at least coördinate with efficiency of management, all of the diverse medical activities?

Undoubtedly great good will come through educational publicity by the development of the National Medical Museum in Washington, an institution which, until recently, has been conducted with an appropriation of but \$5,000 a year. It is true that the officers in charge have accomplished much with this meager sum. They have maintained a record of the progress of medicine of past ages and have accumulated many valuable historical specimens. The accumulations of the present war will make the collection modern, and one of the best in the world. I believe that these medical records of the war will be of the greatest value, not only to the glory of medical accomplishment, but also as a means of interesting and educating the public in scientific matters pertaining to health and disease. The museum now houses the splendid medical library of the Surgeon-General's Office. We can visualize a series of like departments, one to be devoted to the missiles of the present war and the character of wounds produced by them, fully illustrated by plaster casts, wax models, and drawings; another

department to show all the diseases and injuries of bone, with methods of repair and treatment; another department to represent the diseases and injuries of the respiratory system; another, the nervous system, and so forth; each one amplified by animated drawings and moving pictures which will mark an epoch in the teaching of preventive medicine, and especially of surgery. There will be a department to demonstrate all the diseases common to man and animal, also those in which insects are the carriers or the immediate hosts for the diseases of both man and animal. In this department will be taught the prevalence, dangers and prevention of tuberculosis, glanders, actinomycosis, and so forth, as familiar types of a large variety of diseases, and showing the disappearance through control of yellow fever and malaria. The dentists will have a department in which to demonstrate the dangers of focal infections as the cause of chronic and recurring diseases, and to show the results of the neglect of teeth, dangerous types of dentistry, and the best recognized methods of treatment. The department for the curious anomalies and freaks of nature, now the sensational feature of the institution, will be shut off from public view and used only for teaching purposes.

It is probable that the recent graduate in medicine is but 30 per cent efficient. Realizing this fact, some of our advanced universities do not give a degree until after the completion of one year's hospital service.

To raise our standard of medical instruction and organize a trained Medical Reserve Corps, 10 per cent (approximately 200) of our medical graduates each year should enter the Army Medical Corps for practical instruction for a three-year period with lieutenant's pay the same as at West Point. Nine months should be given to military instruction and field service; nine months to public health service, sanitation, and hygiene; nine months to graduate work, and a like period to hospital intern service. If this plan could be developed, a wonderful regular Medical and Reserve Corps would be the result.

The Walter Reed Hospital, built and named in honor of that great martyr to medical progress, should be made the most efficient hospital in the country, and one in which standards of medicine should be established. This hospital, for the most part temporarily constructed, has a capacity of 3,000 beds; it should be replaced largely by permanent construction. Millions of dollars have been spent in Washington by Congress and by the district boards for hospital treat-

ment and maintenance; hundreds of thousands of dollars are spent each year. Surgeon-General Ireland is endeavoring to coördinate the hospital work, the medical instruction, and the laboratories of the museum. It is highly important that he should have the support of the medical profession. While it will cost several millions of dollars to develop such an institution, it will repay many times by the direct return in increased efficiency in the care and protection of our American army, and, through education, in the care and protection of the health of the American people.

## THE RELATION OF MOUTH CONDITIONS TO GENERAL HEALTH\*

C. H. MAYO

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I wish first to say that I am highly honored by the request of the officers of the Minnesota State Dental Association to present at this meeting an address on the subject of mouth infections from a medical standpoint. It is my intention not so much to talk to the dentists, as to speak for the benefit of that small member of society, the child, a subject on which we seem to be in hearty accord. It is not necessary that the dentists of the Northwest should be told how to conduct their business. We have in the middle West the best dentists in the United States. We have here at our University a great school; I don't believe there is any question of its being the best in the United States, and that means the best dental school in the world.

I wish further to state that we of the medical and lay professions are deeply grateful for this opportunity to meet the enlightened and progressive members of the dental profession of Minnesota, men who believe in the art and science of their profession sufficiently to attend such meetings, and who are also desirous of being active participants in all measures that tend to the development of their calling. A few years ago in an address at one of the Dental Association meetings held in Chicago, I talked on preventive medicine and said that the next step in preventive medicine was up to the dentists, and propounded the question, "Will they do it, will they make good?" And I wish to say tonight that they have within the last four years made more progress in their profession than the members of any other profession in this country. I will give them that credit.

One hundred years ago the neglect of dentistry by medical men led to its development as a special study, yet the relationship was recognized by some. Dr. Benjamin Rush, one of the men who signed

\* Presented before the Minnesota State Dental Association, St. Paul, February, 1919.

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the Declaration of Independence, reported a case of rheumatism which he cured by the removal of a diseased tooth. I have always believed that dentistry should have been a legitimate branch of regular medicine, since it is quite as important that dentists should have a general knowledge of disease as it is that physicians, who, after graduating, turn to the specialties of the eye, ear, nose, throat, skin, and other similar divisions, should have it. While it is true that the dentist should refer many patients to the physician for medical examination, it is also true that the physician should refer many more to the dentist for the good of the patients.

At a meeting of the National Association of Dentists a few months ago 7,500 members registered. This is 2,000 more members than are usually in attendance at the meeting of the American Medical Association, and when we realize that there are less than 47,000 dentists in the United States, it certainly indicates the most encouraging enthusiasm and interest.

The home of dentistry is in this country, and the memory of William Black, the father of modern dentistry, has been perpetuated by a statue erected by the National Association. There can be no disparagement of the only profession that has been received with honor throughout Europe, where on every hand one sees the sign "American Dentist." The American army was the first to have its dentistry taken care of. Our chief, General Logan of the Surgeon General's office, was instrumental in increasing the number of commissioned dentists from one for 1000 to one for 500 enlisted men. Thus the mouths of our soldiers that were shown to be so much in need of hygienic treatment were adequately cared for.

The dentists deserve great credit for having created the Research Institute of the National Dental Association from their own funds, recognizing that only by research can any advancement in the profession come. I was greatly honored by being made a director of the Association. Heretofore, there has been but little research in this line. The few institutions standing out prominently as doing this work are the Forsythe Laboratories in Boston, one in Rochester, New York, that was developed by the generosity of Mr. Eastman, and one in Rochester, Minnesota, supported by the Mayo Foundation in affiliation with the University of Minnesota. This work is not intended to include general dentistry. It is conducted primarily for the purpose of research, and to show how the best service can be given.

No dentistry is done, only the surgical work required when diseases are found to be caused by focal infections. The dental research work conducted by the University of Minnesota by Professor Hartzell was made possible through funds donated by the National Board of Dental Research.

Dentists have then, to a great extent, taken the place with the people of the old family doctor who has disappeared, and their clientele calls on them at regular intervals for examination and advice. In the great progress and broadening of medicine it has become impossible for any one mind to grasp the science in its entirety and to be able to practice dentistry with full justice to the sick, as was done a few decades ago.

Team work and organization only will make new medicine possible. We have approximately 140,000 physicians licensed in the United States. The laws passed in the various states to raise the standards of medicine were brought into effect wholly by the efforts of the medical profession. These laws were undoubtedly for the benefit of the people. Of the total number of physicians registered, many thousands were incompetent, many thousands were old or retired, but of the active members, 35,000 joined the army. These, with the dentists who enlisted, made the army life from the training camps to the dangerous fields of battle in France a safer life than that of the civilian.

War has done much for the world, and especially for the United States. It is almost unfortunate that it could not have continued for at least another four months, as we were on the verge of a wonderful national unity with methods planned for the amalgamation of our foreign population into true American citizens. Among the many valuable lessons learned, none has been more valuable than the knowledge obtained by General Crowder's 5,000 examining boards for the draft, on each of which were one or two of the older physicians. As a result of these examinations it was shown that more than 31 per cent of our young men in the third decade of life were physically unfit to participate in army life, and that the causes of these defects were largely preventable. In some states hundreds of young men were incapacitated because of contagious trachomatous eyes, and in some states many thousands had hookworm and various other diseases.

The American people were appalled by the proved conditions reported from the camps with regard to minor defects due to preventable disease, to say nothing of the fact that an enormous number

of soldiers were obliged to sign their names with a cross, and that many thousands born in this country could not speak the English language. This shows some of the defects of democracy in which the average thought is only that of the average people, and it indicates what is necessary in the effort to amalgamate our people. They must be protected as to their health, they must be educated, and later they must be given a living wage in order that they may be happy and self-respecting and thus of value to themselves, to the state, and to the nation.

For many years the medical profession labored alone, almost fruitlessly, for pure water, for pure milk, for the better sanitation and hygiene of the homes, and for the protection of the industrial worker against preventable accidents. Within the last few years labor has become a power, and the industrial workers themselves have improved their conditions. Because of the rapid and expensive turnover of labor with its shortage and its high costs, they have had willing support from the managers of industry. These are changes which are only fair and just, and in accepting them we shall not be driven to make them in our more thickly settled communities by that tyrant against law and order, Bolshevism. Our entrance into the war came just in time for national reorganization.

Good health is an essential to happiness, and happiness is an essential to good citizenship. In America too much of our educating is done at the top and at a time when people are too old to accept changes. Bismarck said, "Give me the child from seven to fourteen to educate and I don't care who has him afterwards, they will not change his early training." This is a true statement and indicates a reorganization of our educational system,<sup>6</sup> which has remained unchanged for many generations. In other words, we must advocate vocational education. The student has the right to be educated along the lines of his adaptability, and thus be enabled to make a living. Insofar as possible during the period of his education, his health should be protected, since his knowledge of how to do this for himself is as deficient as it is of any other branch of education.

The problem before us is to make an effective appeal for better conditions in the lives of the children to the responsible and tax paying persons, many of whom have no children or whose children are now grown. The appeal should be made especially to persons who did not themselves have such advantages and who are proud or com-



placent over the position they now occupy in society without it. In this connection it is always best to appeal to the women of the nation, who have indeed become a power. Baby welfare publicity must come; it should be made an essential part of the education of girls and mothers. In Minnesota the baby mortality rate is low, yet it is twice as high as the mortality rate of our soldiers in France. An unhealthy child makes a poor student whose frequent absence from school and backward education make him more readily susceptible to criminal influences.

Children pay little attention to mouth cleanliness, especially to the care of the teeth. Parents did not receive much dental attention and they do not realize the need for this care of their children. Medical inspection is now an accepted part of the school curriculum, and in the large cities some dental inspection and care is also given; medical inspection protects others against infectious diseases while the work of the dentist is for the good of the individual. The school nurse is an essential to a good school in order that the health work may be carried on effectively.

A certain degree of socialized medicine is inevitable for the future; it is for the good of the child during his school life, for the good of the poor at all times, and necessary for great industrial organizations. Beyond this, such care, except temporary charity as a gratuity, tends, I believe, to lower the standard of self-respect of the citizen. It must be difficult to maintain one's standards while compelled by various vocations to live from gratuities, and yet the tipping system is increasing throughout our country. Our legislatures and congressmen will be largely to blame for the results that accrue from the legislative tipping of our glorious soldier boys who are now to have their patriotism placed on a monetary basis. We, the people, are also the state, and while we must admit that there may be a great disparity in the income results of labor, the fundamental cause exists in the failure in the education and care of the people of the nation during childhood or the education and protection of immigrants.

The allotted years of man are three score and ten; a few men live longer, but a vast number live a much shorter period. Largely through the efforts of preventive medicine during the last three decades, about twelve years have been added to the average life. While more persons do not reach old age, more do reach middle age, and the greatest gain is made in saving the lives of mere babies. The cause,

then, for the high death rate of persons between forty-five and sixty years becomes of the utmost interest to us. Why do we often read or hear of men over fifty-three years of age dropping dead on the street or being found dead in bed? An enormous number of such deaths were caused largely by preventable conditions due to the mouth.

Bacteria must have their own field for growth. Upon the farm the seed of the smart weed grows upon the black soil, when wet; but after the farmer has tilled it, and drilled it and cultivated it the smart weed will not grow; the bacteria necessary for its development have been destroyed. The sandburr is blown over the fields, and if it lights on the wet, black soil that fed the smart weed it will perish and die; it needs the dry sand. The bacteria so necessary for it are found only there. These bacteria keep reproducing themselves they constantly divide and multiply if they have the particular food necessary for their development, but as this food becomes exhausted they ultimately are destroyed.

For centuries past, the history of man, his civilization, his wars, and his study of medicine record the same diseases we have today. The few new ones may possibly not be new, but only conditions recognized and separated from confused groups by greater diagnostic skill and knowledge. The description of symptoms has been recorded and passed on, enabling the various diseases to be recognized. Disease was thus studied as a whole in its effect upon the individual. And we thus have the different methods of treatment, Christian Science, osteopathy, and various others; and I admit I tolerate these because it is necessary to have different methods of meeting and treating the different types of persons. There are lots of people who think they are sick who are not sick. Laws should be enacted requiring a fundamental knowledge of general medicine and of disease, of chemistry, physiology and anatomy; only those who have such knowledge should practice medicine.

The old struggle for existence has caused a great change in the face bones. From lack of use the jaw has gradually receded, and instead of the protruding jaw of prehistoric men with space enough for all the teeth, our last molars or wisdom teeth are now almost crowded out. They do not help us in eating our food. We do not need them; they are often impacted or do not erupt. With the modern preparation of fine flours and foods without enzymes or husks, in a short time we probably shall be like chickens and require gravel in the place of teeth.

Since the discovery of the microscope, progress has been made in the exact study of the changes which take place in the individual cell. The cell is the basis of all life, its life action being a chemical one or a response to an irritation. The new basis of study has advanced our knowledge of disease in its effect on certain cells of multicellular life and has led to the discovery of the larger types of unicellular organisms. Staining effects on secretions and tissues have disclosed the unique world of unicellular organisms—the true chemists of the world, the builders, scavengers, destroyers or converters chemically of both organic and inorganic structures, which are truly the first life in the world, immortal and without which universal life would cease. These bacteria which exist so universally are always ready for action in suitable environments; those in the air are ready to carry on their chemical work in decaying vegetation, in causing infections, in making vinegar, alcohol, yeast for bread raising, in souring milk, curdling the various cheeses, and for countless activities.

Life does not occur without life. Unicellular life exists without death. To multicellular life death comes as a natural limitation to both plant and animal that are given the power of regeneration in perpetuation, although their death may be hastened by unicellular destruction. The life history is known of but few of the countless types of microbes of the world. Many of these which expend their activities in the body locally or generally are well known in their relation to disease, and if they are not controlled or directed for good they may run riot in destruction.

In agriculture the bacteria are soil solvents, also converters of nitrogen in the soil or from the air for plant growth, in result, much the same as those obtained by men electrically. Soils are controlled by adding moisture or removing it by tile drainage, by adding lime or various fertilizers which change the possibility of plant life by changing the environment for myriads of soil inhabitants. The agriculturist or horticulturist has a working knowledge of many microbes, the rusts, scales and fungi of destruction, that cause disease of grains, trees, and plants, and are prevented and treated by sprays and fumigation should disease occur. The government spends millions of dollars in this work, and in the effort to prevent foot and mouth disease, hog cholera, tuberculosis, anthrax, spotted fever, hemorrhagic septicemia, and many other diseases. If this work were wholly effectual it would save our country billions in wealth each year.

Infection of another form is transmitted by insects in which the insect serves as a temporary or intermediate host for a transitional development, for example, of lice, mosquitoes, ticks, and so forth. Here again the government spends millions in eradication and prevention. One thousand dollars is spent in the protection of the animal life of this country to one dollar for the protection of human life. There is but little question that the government, like the law, is readier in the protection of property than in the protection of human life, and theoretically we, as a part of the government, should have the knowledge to protect ourselves; therein comes the need for education and opportunity. We have as portals of entry for the disease germs which afflict the body, the mouth, the openings of secretion, wounds, both punctured and incised, and the bites of insects. The mouth is the great portal of entry of germs from the air, food, water, and filth. In civilized countries the insect carriers of disease are fairly easy of control, yet the clothes louse was a great trouble to our army as a carrier of typhus, trench fever, foot disease, and so forth. The yellow fever mosquito carrier is on the verge of extermination. General Gorgas, whose work made possible the construction of the Panama Canal by converting a pestilential area into one of the safest zones, is now in South America with a group of scientists sent by the Rockefeller Foundation, endeavoring to eradicate the yellow fever from the world for all time. Science and education have done much but education still lags.

I shall not discuss the general diseases, such as fevers and infections so well known to all of us, nor the effects of the chemical destruction of bacteria in wounds with their toxins, further than to state that the cure of any disease or infection depends on the reaction of the body in fluids and cells to the irritation which develops so-called antibodies or chemical solutions as germicides or cells as destroying agents of bacteria with an increase of repair cells.

Bacteria have a definite chemical formula. Carrel and Dakin, as a result of war work and research, developed chemical solutions which, under certain conditions, combined with bacteria and destroyed them while forming other chemical compounds without the destruction of tissue. The well known facts concerning the immunity of the body, generated in the destruction of disease germs, which prevents the second acquiring of the disease were made use of in raising the threshold of body defense against typhoid. Colonel Russel deserves credit

for his pioneer work in checking this disease in the American army. A moment's digression here is of importance in order to state that the great factor of disease which usually brought the wars of past ages to a termination was an unrecognized agent. Ill health was not a factor in this war because of the marvelous advance of the science of medicine. The prevention of disease was the most effectual the world has ever seen in war or civilian life. In the War of the Crimea 250 of every 1000 soldiers died of disease each year, in the Boer War the British had 9000 deaths among 56,000 cases of typhoid. In our Spanish War we had 20,000 sick with typhoid in five months in the training camps; we lost 353 from injury and over 8000 from disease.

Had it not been for our so-called influenza, the greatest plague the world has ever seen, medicine would have been supreme in its record in the great war. This plague caused more than six million deaths, many crippled, and great financial loss; more than 350,000 died in our own country. The excitement and lottery of war, however, prevented the panic that would have occurred at any other time. A study of the causes of death in influenza led to extensive use of the same methods of protection which have proved so effective in typhoid, tetanus and pneumonia. The reports of thousands of cases in which the vaccines and serums were used show the most gratifying results. The few who decried their use had little experience with the disease, did not use the remedy at all, or were ignorant of the methods of similar work in modern medicine.

The chronic recurring diseases of which men die in middle age have been the study of the last few years. In the past people were subject to rheumatism, spells of heart disease, recurring attacks of lumbago, muscular rheumatism, sciatica, or neuritis, iritis, hemorrhages in the retina, and so forth, due to mouth infection in the large majority of cases. They looked on themselves as extraordinarily susceptible and felt sorry for themselves; they sent for the doctor to help them live more comfortably through the period of expected disability, they visited the springs or sought a change of climate. Except endocarditis and bone lesions of children, which are principally caused by mouth infections, the diseases just referred to are diseases of middle life. They are bacterial in origin and the causative bacteria are those common to human and animal life. Nearly all who suffer from them have a small lesion or focus which from time to time delivers bacteria into the blood, and they are carried by the blood

stream to the previously weakened vulnerable spot. Again the recurrent disease is produced and runs an acute or chronic course, developing immunity by reaction, and making improvement for an indefinite but not permanent period. The curious, sudden relief from maladies caused by such local foci of infection led to the recommendation of many eccentric remedies, such as the carrying or wearing of a rabbit's foot—the left hind foot I believe it is—dried potato, rheumatic finger rings, and the use of various dopes internally and externally, or, when the patient felt absolutely helpless from lack of knowledge and results, he took to prayer.

We are hosts to innumerable bacteria on and in the skin whose presence is recognized when continued irritation occurs. Myriads of microbes enter the mouth, and more than sixty varieties make their home there, not all at once, but in harmonious groups. Our intestines are always well supplied with microbes. The blood is also a field for harboring and transmitting a great variety of germs, but many of these organisms are harmless if they mind their own business in their proper place. In typhoid, pneumonia, and other acute conditions, specific organisms are found in the blood, while spirochetes, malarial plasmodium, and many other organisms live in the blood for years, some giving but few symptoms. Some bacteria require the chemical affinity of the nervous cell tissue, possibly through its high carbon dioxid content, and certain definite results occur from infection with the germs of poliomyelitis or meningitis which locate only in the nervous system. These create acute conditions, are destructive, and afford an immunity; others grow in nerve sheaths, joints, muscles and iris, and give recurring exacerbations after an apparent recovery. Such germs are harbored in the lymphoid tissue of the mouth, tonsils, and adenoids, but because of increased opportunity they develop more often in diseased gums, dead nerve pulps of teeth, and apical or root abscesses. In fact the tonsils are often infected from bad teeth. There is no pain in the tooth with a dead nerve. The bacteria are pumped by pressure into a vein, occasionally into a lymphatic, delivered into the blood stream, and carried about the body to be thrown out of the system, destroyed, or to locate in a vulnerable tissue which will become more susceptible to recurring attacks from a similar cause. The devitalized tooth, the crowned tooth, and the tooth with a dead pulp are a menace, and are now under investigation experimentally and clinically.

Our system may at times become allergic to bacteria of certain types, as each type requires a biochemic factor in order to obtain a foothold; once located, however, they prepare their own chemical environment, and are most difficult to dislodge without the surgical removal of the involved tonsil, tissue, or tooth. Rosenow, in cases of acute hemorrhagic gastric ulcer, acute appendicitis, neuralgia, and myositis, has been able to reproduce the lesion in animals by injecting cultures of bacteria taken from diseased teeth, from infected cavities, and from pyorrhea.

The greater number of persons between the ages of 53 and 60 who drop dead, or are found dead in bed, are not the patients known to have heart disease but those who have chronic, painless infections that have caused a bacterial involvement of the heart muscle, and in whom the nerve nodes of the heart may at times become a sudden associated factor of danger. To discuss these questions with older persons who are affected in this manner will do very little good unless they are really sick or unless we can stir them up to help prevent similar trouble in their children or the children of others.

About 85 per cent of children have infections of teeth, tonsils, or adenoids, curable and preventable. William Black has said that one-fourth of us have septic mouths at twenty-five years of age, at forty-five nearly 90 per cent are septic and after fifty practically all mouths are septic. In the examination of the higher officers in Washington for overseas service, I usually found that those with good dentures were well, and that those with bad dentures were not well, and showed the effects of chronic infection. They were usually debarred from foreign service.

We must at least do what we can in our own communities for the betterment of the child. Every large school system must have the school nurse, and a whole time health officer who can, with the volunteer aid of local dentists, which is always to be obtained, look after the examination of the children. I have never had any trouble in Rochester in securing free examinations and glass fittings, and free operations on tonsils and adenoids or teeth for all poor children. It is inevitable that medicine will become more or less socialized as it is in England, and justly so, for the care of the children and the care of the poor. Old age, health insurance, the workmen's compensation insurance, and pension will also come, but such organizations are not satisfactory as a cure. Their aim is to enable people late in life to

recover from the bad educational conditions or unnatural conditions of labor incurred in their youth. Our nation's obligation is to give the same care and expense to the maintenance of the health of our people as it is now giving to agriculture, animal husbandry, commerce and labor.

Medicine in Washington is now a charity, conducted under about eighteen bureaus and boards, including all the cabinet officers, none of whom will relinquish his control or co-ordinate the work; thus, as a whole, their endeavors with medicine are small and inadequate. We need a cabinet officer of health.



# THE RELATION OF CANCER TO THE PROLONGATION OF HUMAN LIFE\*

W. J. MAYO

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## INTRODUCTION

America is confronted by the problem of reconstruction following war. How may she best meet international competition along with failing immigration and an exodus of temporary residents who are now returning to their European homes with their savings earned in America? No one among us can be so mean of spirit as to desire the American laborer to return to pre-war conditions, but rather do we all desire that the laborer and his family shall be well housed, well clothed, well fed, and that his children, the future American citizens, shall be well educated and equal to grappling with the problems of their time. By laborers I mean all those high or low who are engaged in productive employment; not only men but women who, under changing conditions in this country, have become an important part of the labor supply. America must compete in international trade with countries which, devastated by war, contain peoples willing to work long hours for small pay, under labor conditions which we hope never again to see in this country. Successful competition demands efficient production.

There must be a reduction in this country of the 200 per cent unproductive man to a minimum. Every person who is fulfilling an unnecessary function between production and consumption is a double liability, inasmuch as the labor of another is required to maintain him, and what he might produce were he profitably employed is lost. This parasitic class is a great cause of social unrest in America.

\* President's inaugural address, Clinical Congress of American College of Surgeons, New York City, October, 1919.

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## MEDICINE AND THE PROLONGATION OF HUMAN LIFE

In the work of the medical profession lies the best hope for the future. Since the close of the Civil War fifteen years have been added to the average length of human life. With present knowledge and present conditions, fifteen years more might be added to the life of man in this country within the next twenty years. It is certain that ten years will be added, at the most productive age from the standpoint of industry, and will greatly aid in maintaining our position as the most productive nation. When I was a boy it was difficult for a man of forty to find a new job, and for a man of fifty it was practically impossible. Today the older men are great assets to the country. In the prolongation of their lives, their skill and experience in their particular work counts for much. They are less inflammable, they have family ties and responsibilities—they have something to lose—so that they are less under the influence of the violent agitator. If, as a nation, we advance the time of production for each person ten years, we can well afford to shorten hours of work and improve living conditions, and we shall be able to compete with those countries in which long hours and poor living conditions shorten human life, and eventually decrease production and increase social unrest.

The introduction of potable water has made prohibition possible. Prohibition will enormously increase production. In Vienna the per capita consumption of spirituous and fermented liquors was reduced 40 per cent following the introduction of a pure water supply from the mountains. The failure of Italy and France to supply potable water necessitates the continuance of wine drinking, just as in Germany the use of beer will continue. If one traces the temperance movement through the states of the Union, he finds that it was not the appeal to the self control of man which was behind this great movement, but the advent of potable water.

Alcoholic drinks loosen the inhibitory control which civilization has imposed over the primitive impulses of man. Crime, accidents, and social diseases too often have had their origin in the abeyance, through alcohol, of individual self control. Pure water has eliminated typhoid; wholesome food and better living conditions which go with reduction of poverty will check tuberculosis, and better care of focal infections in the earlier decades will prevent many deaths in later life.

## SURGERY AND THE PROLONGATION OF HUMAN LIFE

The arch enemy of middle age and beyond is cancer, and our measures both for prevention and cure have not advanced in proportion to the increasing need. One woman in eleven and one man in thirteen die with cancer, and this proportion of cancer deaths will be maintained in the enormously greater number of persons who reach the cancer age. We must spread more widely the knowledge that chronic irritation is the great underlying cause of the disease. Whenever a certain type of cancer exists in a race of men or in a country with great frequency as compared with other races or countries it is due to a single cause, usually a social custom. Good dentistry has eliminated a percentage of cancers of the jaw due to the irritation of defective teeth. Cancer of the lip and tongue is on the increase as the habit of smoking is on the increase in both sexes. It seems to be a well established fact that in the countries in which the breasts are allowed to remain exposed to the air without covering, cancer of the breast is extremely rare and the incidence is in direct ratio to the amount of covering of the breast and the pressure exerted on it.

Thirty per cent of all cancers in men and 21 per cent in women are in the stomach. The influence of drinks too hot to be held comfortably in the mouth in the production of the chronic irritation which precedes the development of gastric cancer seems probable. Unfortunately, we know less about the causes of cancer of the large intestine and rectum. Diligent search should be instituted to enable us, through knowledge of local causes, to reduce the number of such cases.

*Operation for cancer.*—The majority of cancer patients come to operation too late to be cured. We cannot always demonstrate inoperability in a given case and therefore operation must be done in many questionable cases to give the patient the benefit of the doubt. The mortality in the favorable cases, of resection of the stomach, for instance, is low, but some of the most extensive resections result in cures, although with a greatly increased risk. The paradox of increased experience accompanied by higher operative mortality and a smaller percentage of cures is seen; the explanation lies in the increased operability. The surgeon who reports only percentages of operative death rate and of cure without stating operability, gives us little information. We found that when we operated on only about 25 per cent of the patients with cancer of the large intestine and rectum, the

mortality was about 8 per cent and the cures of the patients operated on about 50 per cent for a five year period, but only 13 of the 100 patients were cured; 75 were considered hopeless at the time of examination and were not subjected to operation. Gradually the percentage of patients operated on was increased. The mortality advanced to an average of 12 per cent; the percentage of five year cures dropped to 37 per cent, but we had 27, instead of 13 of the total 100 patients examined, alive at the end of five years.

I have been impressed with the fact that too little attention has been paid to traumatic transplantation of malignant cells during operation. Rough handling of the growth loosens cells which may become grafted on any surface denuded of its normal covering. A considerable percentage of adenocarcinomas of the ovary is due to spontaneous grafting of cells having their origin in cancer of the stomach. These cells are grafted onto the break in the ovarian surface due to the discharge of the ovum, and the secondary infection in the ovary, by rapidity of growth, may mask the primary disease. Transplantation may occur by gravity to the bottom of Douglas' pouch, the malignant cells becoming attached to the terminal epiploic tags. This produces the typical nodules so readily noted on rectal examination, and which make possible a diagnosis of metastatic carcinoma and inoperability even when the primary focus is unknown.

In our early cases of vaginal hysterectomy for cancer of the cervix we rarely had a cure. The carcinomatous cervix was grasped with vulsellum forceps, traumatizing the tissues during the removal of the growth, and local recurrence resulted. We then began doing all vaginal hysterectomies with the cautery knife and many five-year cures were obtained. The cautery method has a field of usefulness in selected cases. We found that the excessive dilatation of the vagina, preliminary to the use of the cautery, made many fissures in the vaginal mucosa. In two of our cases carcinoma developed in these vaginal fissures from cells deposited there, although there was no recurrence at the site of the original neoplasm.

Carcinoma of one wall of the rectum, exercising eroding pressure on the opposite wall, may cause secondary growth. In carcinoma of the large intestine, by reverse peristalsis, carcinoma cells may be carried upward and become transplanted above as well as below the original growth. In one of our cases a preliminary colostomy was performed and at the end of two weeks, while there was still a little granulating

surface around the colostomy wound, the rectum was removed from behind. Carcinoma cells were evidently detached, carried upward, and deposited on this prepared field, with the result that secondary carcinoma occurred, which was confined to the margin of the colostomy wound. Operative methods must be devised that will more effectively prevent cell transplantation as well as the traumatic detachment of cancer-infected thrombi into vascular channels, a complication which frequently causes postoperative metastatic carcinoma of the liver and lungs.

*Radium, the x-ray, or the cautery as an aid to surgery in the treatment of cancer.*—The use of various agents to extend operability, prepare the cancer field for operation, and as after treatment to reduce the percentage of recurrences, must be further considered.

The normal cell has three periods of existence: growth, function, and degeneration. The normal cell, in the first period, undergoes division for the purposes of growth. During the period of function reproduction is most active. The malignant cell has no period of function, its entire reproductive activity is thrown into the first stage, and only the embryonic growth cell is produced. The normal functioning cell as part of the community life is protected by the entire organism of which it is a part. The nervous system, the blood, the lymphatics, are all a part of this protective mechanism. The malignant cell has no such protection; it is five times as vulnerable as the normal cell and is treated by nature as a foreign body. Malignancy is the property of the cell; the stroma is not a part of the neoplasm but is the measure of nature's defense.

Malignant cells will sometimes be found encapsulated in the tissues of an operative field from which a malignant neoplasm has been removed. Occasionally through some agency such as trauma or general disease the retaining wall breaks down, and metastasis occurs after many years of apparent operative cure. Radiotherapy destroys cells for a certain distance, but cells are sterilized at a greater distance so that their reproduction is checked, and connective tissue is caused to develop which acts as a barrier to the further extension of the malignant process. Radiotherapy often fails when malignant cells become attached to the walls of the three-coated blood vessels from which they draw sufficient nourishment to withstand its effect.

Radio-active substances give great promise for the future. I would include with radium and the x-ray, the radiant energy of heat. For

some years the x-ray has been used more or less following operation and it is believed that the percentages of recurrences, for example in the skin, after operations for cancer of the breast have been materially reduced by this means. We have greatly extended the use of radium and have obtained good results during the last three years, especially in inoperable carcinoma of the large intestine and upper rectum. A colostomy is made as close as possible to the growth, and through it radium is introduced directly into the lumen of the carcinomatous area. In the stomach, by means of a Witzel gastrostomy and the introduction of a tube into the cancerous area, radium may be directly applied, and the patient can be temporarily nourished by means of a jejunostomy.

Radium and x-ray are more or less selective in their action. Masses and bands of scar tissue are produced which delay the advance of the growth, but make subsequent late operation difficult and often ineffective. Heat is not selective, and the scar tissue resulting, while effective in preventing progress of the cancer, does not interfere so seriously with late secondary operative procedures. Radiotherapy has justly achieved a reputation in the postoperative treatment of cancer. It would appear, however, to have its greatest field of usefulness in preparing a malignant area against wound grafting during operation and its ability at least temporarily to reduce the vitality of the malignant cell. Radiotherapy whether applied as radium, x-ray or heat, sickens malignant cells beyond the area of destruction. During this period of cell sickness their resistance is reduced and operation is most efficient, but operation should not be delayed after radiotherapy since the period of increased cell vulnerability is short and the connective tissue development which interferes with subsequent operation is rapid. By properly combining radiotherapy with surgery, we can increase operability, lower mortality, and increase the percentage of cures.

*Suggestions concerning cancer research.*—It is probable that there is a measure of immunity against cancer in all persons, and that this is sufficiently great in some to prevent them from having cancer. I have on several occasions been unable to remove all of a cancerous growth and, to my astonishment, the patient has remained well for a term of years. A search for the cause of such immunity and a means of increasing it is greatly to be desired. The more primitive and important the function of an organ the greater its immunity. The two

most primitive functions are the maintenance of the body and reproduction. The small intestine is primitive and seldom is the seat of new growth; the large intestine has a short heredity and is a frequent seat of neoplasm. The testicle is primitive and is seldom the seat of neoplasms; the ovary is descended from the testicle, has a short heredity, and is a frequent seat of neoplasms.

The surgery of the past has been concerned largely with gross pathologic conditions. As our knowledge has increased diagnosis has improved, technic has advanced, and pathologic conditions are coming to operation much earlier. Surgery strives by every means within its power to reach pathologic processes before they have become gross, and the time is not far distant when treatment may, in some instances, be applied so early in the stage of deviation from the normal that surgery may be unnecessary.

Abstract sciences are being called to our aid, and scientific facts, apparently unrelated, are beginning to be understood in their relation to medicine. Much may be expected from bringing certain of the abstract sciences, especially physics, to aid biochemistry in giving us a better understanding of physiology and pathology.

In 1828 Brown, the botanist, pointed out that minute bodies of all kinds when suspended in gases and liquids are in constant motion. This movement of minute particles took the name of the Brownian movement. Thomas Graham, Master of the Mint in London, in 1861 called attention to colloids, showing that they are matter in a special state of subdivision which makes each colloid particle an entity, but that except as to its physical state, the matter is unchanged. It has been shown that these colloid particles are endowed with movement and that while they are not visible they are of sufficient size to reflect rays of light, as seen in an ultramicroscope. The movements of the colloids Graham recognized as being the movements described by Brown. Physicists have now shown that all matter is in motion, and that those particles more finely dispersed than colloids have even more rapid motion, but since the tissues of the body are matter largely in a colloidal state, we are interested principally in this type of energy. In colloids there is energy, and when the colloid particles change into a less dispersed state, for instance when a cloud which is water dispersed in a colloidal state in the air gives forth rain, the contained energy of the colloid, if the change is sufficiently sudden, is shown as thunder and lightning. The tissues of the body are in a colloidal state and retain

their form and energy, while the non-colloidal elements of the blood such as sugar and amino acids, diffuse through the tissues, furnishing food which is utilized by the tissue colloids after the manner of an internal combustion engine.

The biochemists have shown that when certain substances are in the colloidal state they are more toxic than when they are in other conditions, and this peculiarity has been attributed by some physicists to the energy contained in the colloid body. Certain substances in a colloid state are toxic, but in other states the same substances have no such property. An enzyme is believed to possess energy in part because of the great activity of its colloidal elements, and thereby to bring about chemical changes. It has been suggested that colloid represents energy in life, as radium represents energy in matter. The physical state of matter may influence those early changes which may result in cancer. The benign cystoid appendix, the escape of its colloidal contents from an aperture in the wall of the appendix into the peritoneal cavity, resulting in grafting of hypoblastic elements upon the peritoneum—pseudomyxomatous peritonitis, myxomatous peritonitis, colloid peritonitis, and eventually cancer—are a series of steps which are rather common examples of those processes which are related to the colloidal state. It might be assumed, perhaps, that the physical activity of colloidal particles attacks the tissues and prepares the field for grafting. Again it may change the nature of the disturbed mucous cells in the cystic contents of the appendix, and thereby set in motion a series of events which result in cancer. Such changes are often seen in the ovary and not infrequently in the mucous surfaces of the large intestine and rectum or any part of the body.

Sir William Crookes, in his attempts to demonstrate the fourth state of matter, exhausted the air from a heavy glass bulb. When certain electric attachments were made, the bulb became filled with luminous matter, and, as Crookes expressed it, "actually touched the border land where matter and force seem to merge into one another." He named this luminous substance the cathode ray, composed of negative electrons, which is the fundamental conception of the x-ray. Crookes also pointed out that when x-rays come in contact with solid matter they give rise to shadows, and that the cathode rays, when outside a magnetic field, always travel in a straight line without regard to the position of the poles. The use of energy in the form of rays



such as radium, x-ray, and heat are examples of biophysics in relation to medicine.

I have neither the time nor the knowledge which will permit me to delve extensively into the fields of biochemistry and biophysics. I wish rather to call attention to the contributions of the abstract sciences to cancer research and to urge more intensive study in these new fields.

# PROTEIN SENSITIZATION IN ASTHMA AND HAY FEVER\*

A. H. SANFORD

A study of protein sensitization as a cause of asthma was undertaken two years ago by Dr. Fricke-Davis, a Fellow on the Mayo Foundation. Her investigations are still in progress and the complete report and analysis of these cases will be reserved until some future time. The present clinical report, then, may be considered only as preliminary and is intended to serve merely as a guide to the study of cases of this type.

The subject of protein sensitization in asthma and hay fever has received consideration at the hands of many investigators during the past few years. However, our work has followed chiefly that done at the Peter Bent Brigham Hospital, Boston, by Walker and his co-workers, June Adkinson and Wodehouse, who have made a thorough and exhaustive study of the causes of bronchial asthma.

About twenty-five papers have been published by this group of investigators. Nineteen have appeared as studies. Studies I, II, and XIX deal with the organisms found in sputum of asthmatics. Study III deals with the evidence of sensitization to the bacterial proteins, as demonstrated by skin reactions. Study XIII, by Walker and Adkinson, is on the relation between the cutaneous reactions, serum agglutination tests, and bacterial examinations of the sputum and nasal secretions in determining what part organisms have to do with bronchial asthma. Study XV is on the treatment of such patients with vaccines made from these organisms. Studies IV, VI, VII, and VIII cover the findings in patients sensitive to animal emanations, the serum, dander, and hair of the horse, and the hair of the cat and dog. Studies V and IX deal with the proteins found in various cereals and their relation to asthma. Study X takes up the sensitization of patients with bronchial asthma to the proteins of animal,

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fruit, and vegetable foods. Study XVI considers more specifically the proteins found in the different parts of plants and the individual proteins of cereals. Study XI deals with the important subject of the relation of pollens to bronchial asthma. Study XIV is on the treatment of patients by subcutaneous injections of the proteins to which they are sensitive. Study XIX has just appeared and concerns the types of streptococci found in asthmatics' sputum. Beside these more fundamental studies there have been interesting reports in Studies XII, XVII, and XVIII. In one of these, Study XII, Walker concludes that complement fixation and precipitin reactions, using proteins to which the patient is sensitive as antigens, have no value in diagnosis, prognosis, or treatment in comparison with the great value of the cutaneous reaction. In Study XVII comparison is made between the cutaneous and intradermal methods of applying tests; the results are decidedly in favor of the cutaneous method. The conclusion is that the skin test is specific and separates closely related proteins, that it is sufficiently sensitive and yet not too sensitive. It is a safe index to proper treatment. Treatment gradually decreases the positiveness of the reaction. The subcutaneous manner of making the test is easy and does not inconvenience the patient. The intradermal test is much less specific and much too sensitive and cannot be an index to proper treatment. It is more difficult to perform and causes the patient considerable annoyance and discomfort. Study XVIII is on the relation of eczema, urticaria, and angioneurotic edema to proteins other than those derived from food. Walker brings out the fact that horse dander, ragweed pollen, or other pollens may be responsible for an eczema or urticaria associated with asthma, and that these patients are very difficult to treat in an effort to desensitize, as very small doses may greatly aggravate the skin condition. The papers other than the "Studies" that have been published cover very fully the matter of technic and preparation of the test substances, the classification of asthma, and the mode and results of treatment.

In several published papers,<sup>20, 21, 22</sup> Walker has classified bronchial asthma into the anaphylactic type and into the non-anaphylactic type. In the sensitive type are grouped those persons who have asthma all through the year, due to the proteins of animal emanations, foods, or bacteria, and those who have symptoms only at certain seasons of the year, due to the pollens that are flying at that particular time.

In the non-anaphylactic type, whether the asthma continues throughout the year or comes only at certain seasons, the cause is attributed solely to bacteria.

Sex, nationality, and occupation play little part in the factor of sensitization, with the possible exception that bakers are a little more sensitive to the pollens of flour than other persons, and that asthma due to horse dander is more noticeable in those who come in contact with horses, such as farmers and teamsters.

Age is an important factor in the consideration of the patient's history. In persons past 40 it is very rare, indeed, to find that protein sensitization is concerned in their asthmatic trouble. The highest sensitiveness in Walker's series was found in 90 per cent, or 27 of 30 patients between the ages of 2 and 5<sup>21</sup>. The preparation of proteins in anything approaching a pure state is a chemical procedure more laborious than is advisable to be undertaken in the average physician's laboratory. The gathering of the pollen is also a somewhat tedious process and necessitates preparation of extracts months in advance of the time of use. For this reason, doubtless, many physicians have believed that while there is much to be learned by this method of testing patients it is beyond the power of the general practitioner to carry out such diagnostic measures. Recently, however, a complete list of proteins ready for use as test substances has been placed on the market, and it is with those that most of our tests were made. The substances are prepared under the direction of Wodehouse so that their reliability is without question.

The technic of the test is exceedingly simple. The patient's forearm is cleaned with soap and water, or alcohol. The skin is wiped dry. A number of abrasions are made through the epidermis with a small scalpel or chisel such as is used in making a von Pirquet test. These abrasions are usually placed five or six in rows. In this way fifteen or eighteen or even twenty-four substances may be tested on one arm, or if a large list of substances is used, both forearms may be covered. Tenth normal sodium hydroxid is a solvent for all the proteins that come in dry form. A drop of this is placed on the abrasion with a wooden applicator and some of the dry protein is removed with the same applicator and mixed with the solution on the abrasion. It is necessary to use only a small quantity of the protein substance. A new applicator, of course, must be used for every protein. Care must be taken that the protein from one abrasion does not in any way

come in contact with another spot on the skin. Usually one of the abrasions is treated merely with the tenth normal sodium hydroxid for a control. Thirty minutes, as a rule, will complete a test. Often in a very few minutes a reaction will be noticed by the appearance of an urticarial wheal, about 0.5 cm. in diameter, with an erythema several centimeters across surrounding the central white zone.

We have used, routinely, a rather large list of proteins of the animal emanations, horse dander, horse serum, cat hair, dog hair, and chicken feathers. Of the foods we have used the proteins of meats, cereals, nuts, seeds, and fruits, vegetable and animal foods, milk, and eggs. In the list of meats, proteins were derived from beef, pork, chicken, salmon, veal, lamb, lobster, clam, and codfish. Milk proteins were whole milk, casein, and lactalbumin. Egg proteins were from the whole egg, egg white, and egg yolk. The proteins of grain in our list included those from wheat, subdivided into protein of the whole wheat, wheat proteose, wheat glutenin, and gliadin. The difference in these proteins and their specificity of action is taken up in detail in Study IX by Wodehouse. Beside the wheat proteins, tests were made with rye, corn, oats, barley, rice, buckwheat, and flax; among the seeds, beans and peas were the most important, and among the nuts, walnuts, almonds, Brazil nuts, and peanuts. The vegetable foods, including radish, cabbage, carrot, squash, lettuce, turnip, potato, tomato, onion, asparagus, cucumber, rhubarb, and spinach, for the most part, yielded negative results. The fruit proteins used were banana, grapefruit, strawberry, and cantaloupe.

Probably the most important group of test substances are the dried pollens. Those in our list are the pollens of ragweed, goldenrod, sunflower, daisy, orchard grass, timothy, red-top, meadow grass, sweet vernal grass, and lilac. We also used as test substances dried bacteria, *Staphylococcus pyogenes aureus*, and *Staphylococcus albus*.

Tests have been made in more than 800 of our cases during the past two years. At one time, a few patients were referred for the test on account of some skin condition, but as a rule no patient was tested unless he was suffering from asthma or hay fever. Of this number, more than 500 were entirely negative in their skin reactions. The reactions of about 100 more were doubtful and a more careful analysis of the history than is undertaken at this time would be necessary to prove that the reaction was of any worth in this group. The remaining patients, more than 200 in number, had definite skin reac-

tions. While the final study of these cases is to be undertaken by Dr. Fricke-Davis, a cursory review of the results at this time brings out some rather interesting data:

Twenty-eight persons reacted positively to some of the animal emanations. The largest number of reactions was to horse dander; 13 have a definite history of being unable to go near horses without precipitating an asthmatic attack; 4 have urticaria, showing further symptoms of their anaphylactic condition. Two patients, entirely negative so far as they knew to the effect of animals on their asthmatic condition, lived on farms so that the history is somewhat doubtful. There were 12 doubtful cases in all; one of these is placed in this group because the asthma came on after the patient was 50, although he insists that he had not ever been able to handle horses. Four of this group affected by animal emanations were definitely sensitive to chicken feathers; one of these is also included in the group sensitive to horse dander. Three of the patients sensitive to chicken feathers might also be included among the food asthmatics, as they were extremely sensitive to egg white, egg yolk, and whole egg, and found it imperative to leave these substances out of their diet.

One hundred persons reacted to one or several of the proteins derived from foods. Of the ten different proteins derived from meats which were used as test substances from six to 355 times there were very few positive reactions, thirty in all. In none of these could meat be definitely assumed to have any bearing on the condition, with the exception of the egg anaphylactic patients sensitive to chicken feathers who also, for the most part, could not eat the meat of chicken. The animal foods, milk and egg, were used hundreds of times and were positive only a few times. The greatest number of reactions was to egg white; 11 patients in all were sensitive to this protein. Whole egg and egg yolk were each positive six times. There were no reactions to whole milk; casein was positive only twice, and lactalbumin only three times. In fact, milk seemed to play no part in the asthma in children whom we saw.

Twenty-five patients had marked positive reactions to grain. Ten of these, however, must be considered doubtful, 3 because of their age, and the other 7 because of the repeated attacks of bronchitis which made it seem that infection was probably the chief factor. There were, then, 15 definite cases in this series. Three of these were of children whose food seemed to be the disturbing ele-

ment. Two persons were very sensitive to flax; they are grouped here among the grain sensitive. The remaining persons gave histories which made it seem likely that they were sensitive to the proteins of cereal foods. Wheat proteose is the most common offender of the cereal group, although rye may give as many reactions. Rice occasionally gives definite reactions. We had one domestic who was sensitive to the whole group and found difficulty in eating "war bread" and in handling the ingredients for making it.

There was a large number of patients, 28 in all, sensitive to vegetable proteins. This group on the whole is negative; Wodehouse pointed out in one of his papers that there is very little protein matter in vegetables, except in roots and tubers. Potato contains a considerable amount of protein. Two persons were probably affected by this substance. One man in particular was reported as being markedly improved for months by leaving potato out of his diet.

Fruits, apparently, have little to do with asthma. In several instances banana gave marked reactions. Twice it was known to be a definite factor in producing asthma. One history was most interesting. This patient was seen five years before the present technic was in vogue. A crude method of testing her sensitiveness to this food was tried. An extract was made and what was thought to be a small dose was injected intradermally. A similar extract of raw potato was used as a control. In fifteen minutes the patient developed an urticarial wheal as large as a dollar about the site of the injection of banana extract and simultaneously became afflicted with a most severe attack of asthma. This left no doubt about the patient's having anaphylaxis for this fruit.

In 365 tests to *Staphylococcus pyogenes aureus* and to *Staphylococcus albus* there was not a single reaction. This is at variance with Walker's findings.<sup>1,15</sup> Specific strains probably should be used instead of stock strains as test substances. Among the large number of negative results that we have obtained, infections surely play a large part in the cause of this respiratory affliction.

Because of the very definite results obtained the most interesting group is made up of those persons sensitive to pollens. As is known by the profession generally and also by the laity, ragweed pollen is a definite cause for so-called "hay fever." This has been facetiously termed "a rich man's disease," as change of climate is the popular method of treating the affliction. Probably the most serious factor in

hay fever is the tendency for the patients ultimately to develop asthma. It must be remembered that all seasonal coryzas are not of necessity hay fever. In fact, there is doubtless a large proportion of "colds" of an epidemic nature during the hay fever season that may be mistaken for this specific anaphylactic disease. Twenty-two patients in our group were sensitive to no pollens but ragweed; 4 of these were doubtful cases, 12 had hay fever only, while 6 had hay fever and asthma. We had one patient who was sensitive only of the pollen of goldenrod. This probably was not a definite reaction as her hay fever was contracted in India and she knew positively that the dahlias growing wild on the hillsides were the offenders. Goldenrod when it reacts probably is an evidence of a group reaction rather than a specific cause of the trouble. Goldenrod was coupled with ragweed in 16 other cases. Only one of these need be considered as doubtful. Eight had hay fever alone while 7 had hay fever and asthma. The histories of these 16 patients with positive reactions pointed chiefly to ragweed as the cause. Two of the patients of the series also had an urticaria complicating their sensitive condition.

Beside the group just mentioned there were 31 other patients sensitive to ragweed in addition to other substances; 11 of these were doubtful; and one of these classified as doubtful, while probably sensitive to ragweed as a cause for hay fever, was proved to be sensitive to an insect powder manufactured by a concern of which he was the salesman. Contact with the powder in the factory precipitated his attacks of asthma, and his skin was markedly sensitive to the substance which was not irritating to a normal epidermis. The remaining 19 persons at all sensitive to others substances were undoubtedly afflicted chiefly by ragweed.

In summary of the groups sensitive to ragweed and other fall pollens 52 cases in all, were definitely positive, 36 with hay fever and 16 with both hay fever and asthma.

Twelve persons were sensitive to summer pollens. Eight of these patients had a definite summer hay fever beginning at the time that timothy pollenates. In 2 the histories were doubtful. In the other 2 the summer and fall pollens were both responsible so that the patients began in the summer with hay fever due to the timothy pollen and continued through until frost killed the ragweed.

The discussion of the treatment must be reserved for the later report by Dr. Fricke-Davis. Walker's reports on his own series are



clear, however, and in the main the findings in our few cases are coincident with his statements. The persons sensitive to animal emanations become desensitized for a considerable period by repeated injections of safe but increasingly large doses of the offending protein.

The cases of persons sensitive to food proteins are difficult to handle. Attempts to desensitize have not met with marked success, and careful elimination from the diet of the offending substance seems to be the chief method of control.

The persons sensitive to pollens offer more promise in the way of treatment. Desensitization as outlined by Walker in a recent paper may be carried out either before the season commences or during the season. By far the best method is to begin at least twelve weeks before the earliest date of pollination, starting with a dilution less than that which will give a positive skin reaction and gradually increasing the dose until a few tenths of one cubic centimeter of a 1:100 extract may be injected subcutaneously. Injections are given at weekly intervals so that a patient by beginning in May may receive twelve such injections before the advent of the autumnal hay fever season. If treatment is instituted during the season, great care must be taken or further reaction may follow. At times, asthmatic attacks may be relieved by such treatment, but results are not so satisfactory as with the pre-seasonal method. A very few patients have been treated at our hands by means of dilutions of the pollen extracts. The patients who have hay fever early in the summer who were so treated received no relief, possibly because treatment was not instituted until the season was advanced. Some half-dozen patients treated before the autumnal season have this year experienced marked relief from hay fever and one has escaped asthmatic attacks, that, too, in a season reported as being exceptionally rich in pollen.

In conclusion it may be said that in spite of the many negative tests that have been made in comparison with the small number of positive results, we still believe that there is something to be learned from this diagnostic method, and that more care in obtaining the patient's history and the careful selection of the type of case to be tested will result in less unnecessary work. It would not seem necessary to test persons to the proteins of the animal emanations unless there is a definite history suggesting an asthma due to this type of sensitization. The tests are sharp and the number of persons in this group is very

small. It would seem unnecessary to use a large number of food proteins in testing asthmatics. A few of the cereals and potato as the chief vegetable would include practically all the food proteins that would react positively in a routine examination of asthmatics. The persons sensitive to pollen form the largest group prominent for positive reactions and their histories will practically always decide the type of individual that is to be tested to the extracts of the various weed pollens.

It should not be forgotten that asthma that develops after the age of 40 is very seldom due to a protein sensitization. A very large group of asthmatics remains in whom the subject of infection should be considered most carefully.

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## THE ORGANIZATION AND METHODS OF CONTAGIOUS DISEASE SERVICES\*

J. H. STOKES

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In the spring of 1918, at the suggestion of Dr. W. J. Mayo, I undertook in behalf of the Mayo Clinic a study of the principles underlying the organization and management of services and hospitals for the care of contagious disease, preparatory to the organization of such a service at the clinic. As a part of this study, a tour of inspection was made of a number of the notable Eastern hospitals for the care of contagious diseases. On the conclusion of the investigation the material obtained was presented before the staff of the Mayo Clinic as a report with recommendations. Subsequently, at the request of the Harrisburg Chamber of Commerce and the Dauphin County Medical Society the same material was reviewed as the basis of recommendations and suggestions made to the authorities of the city of Harrisburg with reference to the contemplated construction of a contagious disease hospital. While a certain amount of my own experience is embodied in the recommendations, the heads of the large services for the management of contagious disease, shared with me in most generous fashion their experience and judgment. It is to the stimulating and valuable comment and suggestion and the experience of Dr. D. L. Richardson of the Providence City Hospital, of Dr. R. J. Wilson, Chief of the Division of Contagious Disease in the New York City Board of Health; Dr. S. S. Woody of the Philadelphia Municipal Contagious Disease Hospital; Dr. D. M. Cowie of Ann Arbor, Dr. Owen J. Mink of the Great Lakes Naval Training Station, and their associates, that this report owes much the larger part of what value it may possess as a summary of methods and ideals in contagious disease practice.

The acute infection problem is one of the most pressing issues in the medical practice of today. The mobilization of great armies,

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the concentration of human beings in vast numbers into small spaces, and a devastating epidemic of acute infection in the form of so-called influenza and its complications have brought the problem home to the public with extraordinary force and directness. If professional knowledge is quick to take advantage of an aroused public interest, a new cooperation between physician and layman will bring about advances comparable to those which war has stimulated in other fields of medical practice.

A hospital for contagious diseases is, like the police, a necessary, though not an unmixed, evil. The principal justification for its existence is the convenience and safety of the well public. The comfort, the convenience, and the skilled treatment of the patient are a second, but by no means a negligible, consideration. In so far as the patient is concerned, such comfort, convenience, and skilled treatment as the hospital provides are scarcely enough to offset the menace of enforced contact with contagious diseases other than the one he has acquired. In so far as the hospital staff is concerned, increased risk can only be compensated for by the provision of every safeguard in personnel and construction, and by increased compensation commensurate with the unavoidable minimum of risk. Any community, and any institution public or private which, for its own protection, undertakes the organization of a hospital for contagious disease assumes a grave responsibility. Well built and managed, such a hospital is an asset. It provides for those of average means the highest type of expert service. Skimped, crowded, cheaply and unintelligently constructed and poorly managed, it becomes a grave public and private danger.

The practical details of all organized care of contagious diseases center around seven principles. These include:

1. *Risk in contagious disease practice.*—All contagious disease practice involves risk, greater than that which occurs in the ordinary practice of medicine and nursing, and greater where the work is concentrated in one place, as in a contagious hospital, than when it is distributed as in ordinary house isolation. The element of risk involves patient and attendant alike. As Dr. Woody has put it, a child, placed on a ward with forty other children who have contagious diseases, is subject to 200 times the risk of acquiring one of the five contagious diseases than if he were kept isolated at home. This risk is accentuated by the lowering of resistance incident to the infection from

which he is suffering. Cross infection is the bugbear of contagious hospital work, and it can become so common in a poorly managed service that no person who can avoid hospitalization for a contagious disease will submit to it. The human element of risk to the staff and patients of a contagious hospital is summed up in the hack phrase that a chain is no stronger than its weakest link. The health, the efficiency, and the life of the members of a contagious hospital staff and of the patients are dependent on the conscience and the technical ability, not of the ablest, but of the weakest and least efficient member of the staff. The element of personal equation, so far as I can ascertain, can not be wholly done away with by any refinement of technic. It can be reduced to a minimum, (a) by construction which so far as possible makes blunders physically and mechanically impossible and which employs the natural agencies of sunlight and fresh air in every department, including living quarters, in the diminution of the risks; (b) by a military stringency of discipline involving the entire medical, nursing, and non-professional staff; (c) by an exact habitual routine and (d) by the employment throughout the staff of persons of a superior type of human intelligence, better paid, better cared for, better trained, and more permanent than the average.

2. *Isolation for diagnosis and on suspicion.*—Contagious disease is usually most dangerous just before and during its onset and in its earlier stages. The source of the danger is twofold: (1) There may be nothing to warn those who surround the victim-to-be of the actual situation and of the danger attendant on contact with him before his manifestations become so definite that warning is given. The carrier problem in such diseases as epidemic pneumonia, meningitis, diphtheria, and typhoid fever, is simply a special phase of this problem. (2) Danger to public and patient alike arises from errors and from unavoidable delays in diagnosis even after the signs become apparent. Time for observation is an essential factor in the diagnosis of certain of the contagious infections, and yet the delay subjects others to exposure, except under conditions of isolation or quarantine. The diagnostic instinct does not exist which can cover with infallibility on sight all the variations in the clinical picture represented by toxic erythema, true scarlatina, and scarlatiniform rubella, or between variola, varioloid and varicella. Blunders due to haste and misinterpretation are inevitable unless special means are adopted for their prevention. The special means which modern contagious disease

practice should adopt are summed up, apart from the employment of various procedures such as vaccination of contacts, in the conceptions of isolation on suspicion and isolation for diagnosis. Adequate equipment for handling contagious disease will give the diagnostician's desire for expectancy and observation as an aid to diagnosis the respect which it deserves, and will, during such a period of observation, protect the patient and the public alike by complete individual isolation.

3. *Detention*.—A patient suffering with one contagious disease may, before his entry into hospital care, have been exposed to another contagious disease whose manifestations do not appear until the patient has been admitted. Such importation of infection must be prevented by a period of observation or detention of every patient on entering, which is sufficiently long to insure that no new infection will develop after he comes in contact with other patients. Such detention must, again, be specifically provided for in construction, equipment and technic.

4. *The transmission of contagious disease*.—The organization and management and the construction of hospitals for the care of contagious disease must be governed by the principles underlying the transmission of the diseases with which they deal. In respect to these principles, anything but unanimity prevails. In general the less that is known about the etiology of a given infection, the more varied are the opinions regarding its mode of conveyance. Two distinctive points of view, however, are recognizable in contagious disease practice, the "air borne" infection theory, and the "contact" infection theory. The theory of air transmission, the older of the two, has in its simon-pure form led to the "pest-house" conception of the contagious hospital. It is this point of view, carried to an extreme no longer justified by modern knowledge, which has led to the building of contagious disease shacks in waste places, and which underlies the horror of contagious disease that is fundamental to the uncritical and ignorant mind. Such a misconception is quite capable, even though medically revised, of depreciating the price of real estate, and of leading to eccentricities of construction such as those of the isolation or reception units of many of the large municipal hospitals. While the conception of air transmission of contagious disease in its original extreme form has no place in modern practice, its revised interpretation is leading to an increasing emphasis on droplet infection in diseases accompanied by marked respiratory symptoms. For example, the

use of the face mask has become a well-established feature of hospital technic, and the placing of screens between even healthy persons, as in the barracks of the Great Lakes Naval Training Station under the direction of Dr. Mink, are recognitions of the fact that under certain conditions infection may be air borne.

The theory of contact infection under the leadership of such men as Chapin and Richardson of Providence, has assumed a more and more prominent rôle in the current conceptions of infectious disease transmission. According to this theory the transmission of contagious disease is accomplished only through actual physical contact with the patient and with articles such as the bed, the sheet, and the pillow, which come most immediately in contact with his person. The air about the patient is considered to be clean and the risk of droplet infection is confined to gross forms such as when the patient coughs into another's face. Under the contact theory of infection the problem of the care of contagious disease becomes a problem of the same order as that of keeping the operative field free from microorganisms, or at least so nearly free that the patient's resistance can overcome the few invaders. Currents of air, their mere presence in the room or immediate locality, lose the significance attached to them in the old air transmission theory, and danger exists only on physical contact with the patient or with his immediate surroundings.

These two theories affect contagious disease practice in two very different ways. Under the old air transmission theory, the infected persons were bottled up as tightly as possible in a quarantined area, all healthy persons were warned to keep away and on the windward side, and the nurse was bottled up with the patient to fight out the question of her own infection on the basis of whatever resistance she might possess or acquire. Air transmission requires unit segregation; all cases of the same type are isolated *en bloc*, as far as practicable, in a separate building and locality.

The contact infection theory, on the other hand, greatly simplifies certain phases of the work, while rendering others more complex. According to this theory it is a matter of no consequence whether two patients with different diseases are in the same room or not, provided they and their immediate surroundings do not come in contact with each other, and provided no carrier takes the infection from one to the other. The prevention of the transmission of infection by carrier becomes the crucial point of hospital management under the contact



theory, and the main effort centers about the technical details of so-called aseptic nursing. On a pure contact transmission technic it is permissible, as in the Hospital for Sick Children in Paris, or in one of the Providence City Hospital pavilions, to mingle on the same floor or ward cases of every type, provided the beds are sufficiently far apart to prevent physical contact, and the nursing and medical staff sufficiently highly trained completely to remove all traces of one infection from their persons before leaving one patient to go to another.

The strict contact infection theory, with its aseptic nursing technic has admittedly failed fully to justify itself in the care of measles and chickenpox, both of which infections seem to be of so elusive and so "catching" a nature as to make air transmission seem almost plausible. Smallpox is still regarded, by Eastern men especially, with a peculiar dread and its rigorous isolation is enforced. Scarlet fever and diphtheria, on the other hand, seem to be entirely amenable to a contact infection technic, and crosses with either of these diseases seem easily traceable to errors in technic. In both of these diseases it should not be forgotten that there is a large native immunity factor which probably is instrumental in explaining the success of the aseptic technic. In diseases in which respiratory symptoms are conspicuous it seems likely that droplet infection should be prominent. Yet in the case of diphtheria there seems to be little evidence of such a mode of transmission, while in epidemic pneumonia recent army work suggests its very great importance. Where so many moot questions still exist, it would seem obvious that the safe and conservative practice will neither be that of air transmission, with its farcical overdoing of precaution, nor that of contact infection, with its reliance purely on technical methods and the conscience and expertness of the attendant. It will be intermediate between the two, and while insisting on the rigorous execution of every aseptic precaution in contact with patients, will none the less interpose every available physical barrier against infection, and utilize every element which can be made to increase individual resistance, and employ the natural agencies of fresh air and sunlight in the destruction of the infecting agent and the diminution of the risks.

5. *Fool-proofing of hospitals and technic; minimizing the personal Equation.*—Contagious disease practice and contagious disease hospitals should be, so far as possible, fool-proof. The necessity is as obvious as it would be in a plant for the manufacture and handling of

high explosives. Fool-proofing contagious disease hospitals and practice means essentially the reduction of personal equation to the lowest possible terms. This demands rules, of course, and their observance; but it demands more, namely, the substitution of a physical barrier against a blunder in preference to a verbal injunction, wherever possible. The adequate carrying out of such a principle calls for ingenuity and sometimes for extra expenditure in construction, all of which amply repay the cost.

Such risk as cannot be done away with by the physical fool-proofing of structure and equipment, must be met, as has been mentioned, by the systematic and constant elimination of incompetent and inept persons from the personnel, and by the maintenance of a discipline which is inexorable in its requirements.

6. *Modern disinfecting methods: soap, water, sunlight, fresh air, steam.*—The older contagious disease practice depends for the destruction of the infecting agent on chemical disinfection. Modern contagious disease practice depends on mechanical and biologic means of destroying the virus and of preventing its passage from the sick to the well. The keystones of the prevention of the present day in this field are soap, water, sunlight, fresh air, and steam. The modern contagious disease hospital consists, figuratively speaking, of plumbing and glass. This in part accounts for the relatively high cost of construction of worth-while contagious hospitals. Yet this consideration should not be allowed for a moment to subordinate the principle to a short-sighted niggardliness. More than one otherwise admirably constructed hospital has suffered a loss of flexibility and efficiency through unwise economy in these fundamentals. Slit-like windows, resembling the ports for archery fire in the walls of ancient castles, inaccessible bathrooms, one to a floor, and rooms without running water are alike anachronisms.

7. *Fluctuating load.*—Hospitals for the care of contagious disease must be constructed so that they may care for wide variations in the number of cases and the types of diseases received. Seasonal variations are marked. In summer a contagious disease hospital, if built apart from a general hospital, must remain largely idle. If poorly constructed it cannot be used for any other purpose. One year an epidemic may make the ratio of measles to scarlet fever ten to one, and throw a ward or building isolation system hopelessly out of commission, while other exanthemas may cut a negligible figure. The next

year measles may be almost unknown and seven other contagious diseases in about equal strength may tax the facilities for isolation. In the third year, a single disease may be pandemic, the hospital may be filled to the doors and prove utterly inadequate to meet the situation. A hospital for contagious disease should be built to something above the average peak-load in ordinary years, and with every possible provision for the highest degree of flexibility in the number of diseases for which it can care.

APPLICATION OF THE FOREGOING PRINCIPLES TO THE ORGANIZATION AND MANAGEMENT OF A SERVICE

*Staff personnel and discipline.*—In aseptic nursing technic the element of personal equation is paramount. Under such technic a careless nurse or doctor rapidly accumulates to his credit a list of cross infections which discredits the whole method<sup>1</sup>. Therefore, wherever the aseptic technic in particular is to be employed a rigorous selection of employees must be practiced. This technic is the only one applicable to the small contagious hospital.

The responsibility for the technical excellence of a service rests in the last analysis on the director; this responsibility cannot be divided. Just as under military conditions and under the dangers of war, discipline places the situation completely in the control of the commanding officer at a given point, so in dealing with the dangers of contagious diseases similar powers must be vested in the executive head of a service. The power to employ and discharge and to approve and disapprove must be completely in his hands. So long as the director's accomplishments and results justify him, he must be a military chief and have summary authority in matters of method and administration over his confrères by common consent, and over nurses, orderlies, attendants, patients, and their friends and relatives. The selection of supervisors to carry out his methods must be made with his approval and he must have power to remove them without appeal. In theory, at least, the way to appeal from the judgment of the medical director of a service for contagious diseases is to accept his resignation. As in the presence of danger in battle, the stringency of military discipline is increased, so in the presence of the very real danger of contagious disease, discipline must have a severity not demanded in the ordinary hospital service, and comparable in medical practice with the completeness with which the surgeon dominates his operating room.

The director of a service for contagious diseases must be a man qualified to meet the exactions of the task. There is probably no single type of medical duty which carries with it more petty vexations than this. In addition to a native tactfulness the director must be a man with the necessary driving force to hold others to the demands of their tasks and with the necessary energy to be constantly on the *qui vive*. He must be able to meet the situation in which an inferior reports a superior for breach of technic as skillfully and yet as energetically as he would the reverse. He must be a detail man, able to carry at his fingers' ends all the intricacies of an elaborate technic. He must make a special study of methods and keep up to date in them. He can never shrink from the disagreeable task of placing responsibility on the person on whom it should rest. There is probably no type of service from which more complaints inevitably arise and which can arouse a storm of criticism and protest in a shorter time than can a service for contagious diseases. It is absolutely no place for an easy-going fellow. It was a matter of the greatest interest to me to recognize in the chiefs of the really famous contagious services of the East a masterful type of personality.

It is widely recognized as a physical and mental impossibility for certain types of nurses and certain doctors to observe the requirements of aseptic technic, just as certain persons are fundamentally unfit to be surgeons. They do not have the instinct for the work. For that reason all persons on the staff of an isolation hospital, from the orderlies and scrubmaids to the director, should enter on a probationary understanding. If they prove unteachable, technically inefficient or mentally unfitted for the work, they should be removed from office promptly and without appeal. There can be no possible excuse for subjecting either patients or staff to the dangers arising from a weak link in the chain, from the moment its unfitness is discovered.

The hospital using aseptic methods should not, in general, admit outside physicians to practice within it, except under staff supervision since they are too often notoriously unmanageable when it comes to technical exactions.

In order to secure a high grade of personal efficiency in a staff, three other elements besides native aptitude and special intelligence are necessary. These are long service, good care, and good pay. Short-term rotating services have at best only a limited efficiency. If they must be compromised with, as in the case of the training of

pupil nurses, the training period must be long enough not only to enable the pupils to learn the method, but also to be of some use after the method is learned. It is generally conceded that a six months period is the most desirable, but that compromise can be made down to the point of three months, and under exceptional conditions, of two months. By exceptional conditions are meant those provided by thoroughly modern hospital construction such as minimizes the risk of cross infection. Moreover, the contagious hospital which houses its staff in dingy and ill-ventilated or crowded quarters, feeds them poorly and overworks them invites disaster.

#### SPECIAL TECHNIC

To study the methods of a number of contagious services is the best way to appreciate the varieties of opinions and methods which exist in this field. A service which is tinged with air transmission ideas will not permit a visitor more than to enter the building without putting on a gown and cap and perhaps a face mask, and will rigorously provide a building for each separate disease. On the other hand, a pure contact system will allow the visitor to walk about the ward of barriered beds at will, provided he does not touch the patient, bed, or other surroundings. It will even permit active carriers to walk about clean corridors provided they keep their arms folded and touch nothing but the floor. At the present time, however, a compromise involving the best elements of both systems would include approximately the following points.

1. Attendants should change from street to short-sleeved duty uniforms on entering the hospital and make a reverse change on leaving it.
2. The infection should be limited to the quarters containing the patient.
3. The aseptic character of all corridors and passageways should be rigorously maintained.
4. Areas and objects as follows should be regarded as invariably infected: (a) The floor; (b) the patient; (c) all parts of the patient's room within reaching distance of his bed and in fact, in many hospitals, the entire room as high as a person can reach; (d) everything with which the patient or the above-mentioned objects come in contact. This includes bedding, utensils, food, discharges from the patient, and so forth.
5. A special gown covering the entire costume should be worn by attendants while they are within the infected area.
6. This gown should be removed, properly handled and disposed of in accordance with an exact technic before the attendant enters a clean area.
7. A cap covering the hair should be worn.
8. A face mask should be worn by persons while on duty in an infected area, especially when attending certain types of cases.

9. All attendants should rigorously cleanse the hands and forearms with soap and brush and running water before they leave the infected area.

10. Any article which has touched one of the above mentioned infected objects should be immediately treated as infected.

11. Every infected object should be efficiently sterilized as follows: Dishes should be boiled, garbage burned, dressings and infectious discharges on rags, burned. Gowns, linens, and clothing should be sterilized either by immersion in sterilizing solution followed by steam laundering, or by steam sterilization with or without subsequent laundering. The body should be cleansed by washing with soap and water; little reliance is placed on disinfectants. When the patient is discharged mattresses and unwashable clothing and bedding should be sterilized by steam or formaldehyd in special steam sterilizers or rooms and subsequently exposed to air and sunlight. The bed should be washed with lysol and water, and exposed to air and sunlight. The room should be scrubbed (the floors and the walls as high as can be reached) with soap and hot water. Radiators, chairs, tables, doors, door frames, door knobs, and so forth should be included in this scrubbing. Fresh air and sunlight should be used in every possible way for the control of infection.

12. The patient should be discharged in such a way as will prevent his infecting the corridors through which he is taken, or his carrying infectious material to the outside.

13. Every patient should be treated individually in a single room rather than collectively on wards.

14. Rooms containing a single type of disease should be grouped in one unit, under a single nurse or a group of nurses who do not care for another type of disease, even though using an aseptic technic.

15. The privileges of visitors should be restricted.

16. Where patients are kept together on wards, even with the same disease, the beds should be separated by sheet curtains or glass cubicle partitions.

17. Crowding either by having too many patients to the room or unit, or too many patients for each nurse should be absolutely prohibited. Crowding spells the complete breakdown of any system of contagious technic and consequent cross infection.

18. Every entering patient should be detained in "solitary" until the longest period of incubation of a contagious disease is passed (three weeks) before he is placed on any ward or in contact with any other person. This is to prevent entry crosses from patients incubating one disease while entering with another.

19. Cultures from the nose and throat should be obtained from all persons entering the hospital as patients or staff, for the detection of carriers; the culture should be repeated on discharge.

20. All female infants should be examined for vaginitis (vaginal smear) and the invariable rule made never to place two female infants in the same room or to allow diapers to be washed by floor nurses.

#### SPECIAL CONSTRUCTION DEMANDED BY MODERN TECHNIC

In the carrying out of the principles herein described, certain special requirements in the construction of a contagious disease hospital must be met. As in the development of technical methods, so in hospital construction, a compromise between extreme views must be sought. Where only average grades of medical and nursing help, for example, are to be obtained, it is unwise to construct a hospital relying

solely on the preservation of medical asepsis to reduce the dangers of handling these diseases. On the other hand, where nurses are to be taught a modern technic a hospital cannot be built exclusively on a unit segregation plan, with one disease in each building, since, in this type of construction, technic easily becomes slipshod and untrustworthy.

The ideals already outlined are to be attained by attention to the following details:

1. By the erection of a hospital or of hospital units of wieldy size, consisting practically entirely of single rooms.
2. By the minimal transfer of patients through corridors. This may be secured by (a) the outside entry to rooms through an open porch and (b) one-story construction so far as the part devoted to patients is concerned.
3. By the "elastic unit" type of planning, which makes it possible to divide a hospital into four, six, or even more units, each composed of two or more single rooms, and so arranged that a given nurse can be limited to the care of a single disease, instead of caring for one patient with one disease and another patient with a different disease.
4. By the provision of abundant porch space, so developed as to be usable as much of the year as possible.
5. By the use of many large windows, glassed doors, and so forth to admit a maximum amount of sunlight and fresh air to the body of the hospital. Too much of the walls of contagious hospitals in the past has been built of brick, and too little of glass.
6. By a very liberal provision of plumbing fixtures and bathing equipment. This should be so arranged as to provide at least one-third of the rooms with individual plumbing facilities, and to give each room access to a tub within the unit of which it forms a part with a minimum of hall traverse to reach it.
7. By the provision of running hot and cold water in each room for proper disinfection of the attendant. This supply must be available without the use of the hands.
8. By the provision of dry high pressure steam for all types of sterilization, except unwashable clothing.
9. By provision of large diet kitchens, linen and utility rooms, arranged in groups on the basis of the unit organization of the hospital, and providing for not less than three diet-utility groups for twenty-five beds. Unwise economy in space devoted to these features is sure to be regretted.
10. By provision for the proper preparation under supervision of entering doctors and nurses and their proper cleansing before exit from the hospital. This requires in general a room for the removal of infected clothing, a bath and a clean room or its equivalent.
11. Similar provision must be made for the discharge of patients.
12. The room unit must be constructed of such materials and in such a way that it can be cleansed with soap and water throughout. This means (a) there must be no unwashable or inaccessible fixtures; (b) there must be no avoidable cracks, corners, or niches in floors, walls or door and window casings, to serve as places of accumulation for infectious material; (c) it must also be so large that it is possible to move about in it with ease and without involuntary contact with any part of the equipment; (d) it must never be crowded to the point where this is made difficult; (e) it must contain a

minimal amount of furniture; (f) it must have a door opening to the outside (porch) and needless entering of the room by the inner door must be done away with by the provision of special windows for observation of the patient.

13. So far as possible the construction of the hospital should be such that it is impossible for a technical error to be committed without its being observed.

14. By the skilful use of partitions, swinging doors, elbow-catches, and signs, it should be made difficult to forget that one is in a contagious hospital, and the temptation to commit technical lapses should be minimized by making the improper action or movement, as nearly as can be, physically impossible.

15. The majority of contagious hospitals treat the dead body as infectious, and provide for the postmortem examination on the premises, and for the embalming and funeral ceremony in a specially devised morgue from which the body may be viewed by the relatives, and then taken away in a sealed casket. There can be no question that such provision is of a sentimental value and mitigates the distressing features of the care of this type of case without injury to the public.

16. Whenever possible, the contagious hospital should take account of the human factor in illness and should make provision for relieving the anxiety of relatives by permitting visits under proper control, and providing even for the attendance at the bedside of the dying. Attention to certain details and devices of construction can assist in this effort.

The discussion of the problem presented by the city of Harrisburg, in which discussion Dr. Woody of Philadelphia participated, brought out several interesting practical details. A contagious disease hospital is primarily a city problem rather than a country or county one. The service of a contagious hospital to a large and rather thinly populated county is a matter of uncertainty. On the other hand, it was pointed out that the modern automobile ambulance has greatly extended the ability of the hospital to meet the needs of the acute case within a radius of from four to ten miles. The ambulance as an extension of the contagious hospital, or indeed of any hospital, has an effectiveness dependent to some extent on the professional skill, judgment, and equipment of the ambulance personnel. A blundering, inexperienced ambulance staff can, by omission or commission, be responsible for errors which no hospital, however complete, can ever remedy. While such a statement is most directly applicable to emergency and accident service, it must be considered in planning the extramural activities of a contagious hospital service.

Modern conceptions of the transmission and control of contagious diseases are doing away with building isolation, and the dissociation of contagious disease practice from the work of the general hospital which has prevailed in the past. The writer agreed with Dr. Woody in urging on the authorities of the city of Harrisburg that they consider their contagious hospital not as a thing to be built apart, but as a part



of a large general hospital. The contagious hospital itself should be constructed in building units comprising twenty to twenty-five single rooms with their diet, utility and administrative equipment, the units being reduplicable as expansion is indicated. There seems no reason why this feature of hospital construction, so well worked out in army practice, should not be applied to contagious hospital construction. There seems, moreover, to be no reason why at periods when the properly constructed contagious units of a general hospital are not in use for contagious disease, thorough cleansing, with a liberal use of paint, should not make a portion of the equipment available for general purposes. This possibility of "taking up the slack in contagious" hospital work by association with general hospitals and using it for other than contagious diseases, will make practical refinements in construction which it has been difficult in the past to get hospital authorities and public officials to consider on the ground that the variations in the usefulness of contagious hospital equipment were so great as to prohibit expensive construction.

The cost of contagious hospital construction will of course vary with the factors which determine building costs in general, including the site, current costs of material, labor, etc. Material economies in the construction of smaller contagious units can be affected by the utilization of the heating plant, laundries, and kitchens of a general hospital. Other economies can be brought about by an intense but discriminating attention to details. For example, a contractor pointed out to me a certain type of matched brick-work on an otherwise well-planned hospital, which without adding materially to its appearance or usefulness had raised the cost about \$100 per bed. Dr. Woody and I concurred in estimating the cost of the ideal contagious hospital of the present day at not less than \$2,000 and probably more nearly \$3,000 per bed. During the period of war inflation of the cost of material and labor, the cost as determined for the proposed Mayo Clinic Contagious Hospital would hardly have been less than \$3,500 per bed.

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## EXPERIMENTAL SURGICAL SHOCK

### V. The Treatment of the Condition of Low Blood Pressure which Follows Exposure of the Abdominal Viscera \*

F. C. MANN

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This work was undertaken for the purpose of investigating under standard experimental conditions all the more important methods of treating a condition which exhibits the clinical signs of surgical shock in order to determine the relative value of the methods. While numerous such investigations have been made, only a portion of the entire field has been covered by a single investigation. Since in the different series of experiments various methods were used to produce the condition called shock it is impossible to compare the therapeutic results.

The method of producing the signs of shock was the same throughout in the present investigation and while the results may not be applied directly to all cases clinically diagnosed as surgical shock, the different methods of treating a condition which presents a common symptomatology can be accurately compared. Since it is obvious that the condition which the surgeon terms shock is due to a variety of causes, it is useless to attempt to find a specific therapeutic procedure, but as the symptoms are usually the same it is reasonable to suppose that some general therapeutic measures will be found.

The method of producing shock has varied greatly with the different investigations. In my work exposure of the abdominal viscera has seemed to afford the nearest approach to the production of shock presenting all the clinical signs.<sup>17</sup> Our routine method was as follows: The animal, a dog, which had been fasted for from twelve to eighteen hours, was etherized in a closed cabinet, incubated, and a constant surgical anesthesia maintained by means of a Connell apparatus. Carotid blood pressure was recorded by means of a mercury mano-

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meter; sometimes the membrane manometer was also employed. After a record of normal blood pressure was obtained, the abdomen was opened and the viscera exposed. The only trauma to which the exposed viscera were subjected was the occasional gentle sponging with dry gauze or changing them from one side of the body to the other. When blood pressure had decreased and remained rather stationary at the desired level, which usually occurred about one to two hours after the exposure of the viscera, they were returned to the abdominal cavity and the wound was closed. After a length of time sufficient in which definitely to determine that blood pressure did not increase, procedures to improve the condition of the animal were instituted. The blood pressure was taken as a criterion of the animal's condition because it affords the easiest method of comparison. All other clinical signs of shock were also noted.

The maintenance of a constant anesthetic throughout the experiment removed the possibility of an error either in the interpretation of blood pressure records or in the general condition of the animal.<sup>19, 20</sup> Anesthetic control experiments were carefully performed, the etherization being maintained at the same tension and for a length of time equal to that of the shock experiments. Practical conclusions can only be drawn from the results which apply to the condition in which the signs of shock were produced by exposure of the abdominal viscera, although it would seem that they should also be of value in a condition of a lowered and progressively decreasing blood pressure. The experiments were acute because it seemed that the therapeutic procedure would be put to a greater test if the animal was maintained under an anesthetic throughout the experiment and because the character of the experiment would not warrant the complete withdrawal of the anesthetic.

The fact should be emphasized that blood pressure which has been decreased and remains stationary below a certain level, and is allowed to remain there even for a very short time, is never restored and maintained by any known method of treatment. We have estimated the pressure below which no hope for restoration could be held as half the initial pressure maintained constant for one hour. In our experiments the methods of treatment, with very few exceptions, proved of no permanent value if the blood pressure had been decreased to less than one half its initial value; this is true regardless of the means by which blood pressure is lowered, for example, by hemorrhage, exposure

of abdominal viscera, and by obstruction of the venous return, such as partial occlusion of the vena cava. Conclusions should, therefore, not be drawn with regard to a therapeutic procedure when it is tried out in an experiment in which the blood pressure has been decreased below one half its normal value and because of the variability of the different animals unless, of course, the animal recovers. We believe however, that it might be of some clinical value if a therapeutic procedure could be found which completely or in greater part restores and maintains blood pressure for two hours, with the animal under a constant anesthesia and with a constant artificial temperature condition, after the blood pressure has been decreased from one third to one fourth its initial pressure by exposure of the abdominal viscera. These conditions were the standards we used in judging the value of the various methods of treatment.

The treatment of shock may be described under four headings: (1), general measures; (2), special measures; (3), the use of drugs; (4), attempts to restore fluid volume.

*General measures.*—The most important general measure in the treatment of shock is the ancient practice of applying heat. The employment of heat is of value not only because shock is commonly associated with exposure to cold but also because the thermogenetic and thermoregulatory mechanisms are impaired. It is probably not true that this impairment of the mechanism which keeps the body temperature constant is the primary cause of shock but the artificial maintenance of body temperature during the period of impairment produces beneficial results. It should be noted, however, that this deficiency in regulation applies to heat as well as to cold and that too much heat is harmful.

In most instances the temperature of our animals was kept almost constant by the judicious employment of an electric heating pad. In some experiments the heat was only applied after low blood pressure had been produced and at the same time the other therapeutic measures were instituted. Except that the blood pressure decreased more slowly when the heat was used from the beginning of the experiment no notable difference was observed in the results of the therapeutic procedure.

In order to increase the circulation around the bulbar centers it is usually recommended that the head be placed in slight Trendelenburg position. Theoretically this should be of value, practically it may be; but in our experiments little effect could be noted.



FIG 481.



FIG. 482.

FIG. 481.—Kymograph record showing the successful use of acacia. *Record I*, normal blood pressure 118. *Record II*, after the abdominal viscera had been exposed one and one-half hours; blood pressure 70. *Record III*, taken thirty minutes after the viscera were replaced; blood pressure 74; 160 c.c. (20 c.c. per kg.) of a 6 per cent solution of acacia in 0.9 per cent sodium chlorid solution were injected (signal A-B); the injection was probably too rapid. The blood pressure increased to a maximum of 84. *Records IV, V, VI, VII and VIII* were taken at succeeding hours after the injection. The blood pressure was 84, 90, 95, 95, and 96 respectively. This is one of the few successful results following the use of acacia in the series of experiments.

FIG. 482.—Kymograph record showing the favorable action of acacia. *Record I*, normal blood pressure 105. *Record II*, after one hour of exposure of the abdominal viscera; blood pressure 70. *Record III*, fifteen minutes after replacing the viscera; blood pressure 68; 100 c.c. (20 c.c. per kg.) of a 6 per cent acacia solution in 0.9 per cent sodium chlorid were injected slowly; blood pressure increased to a maximum of 82. *Record IV*, taken thirty minutes after injection; blood pressure 76. *Record V*, taken one hour after injection; blood pressure 80. *Records VI, VII, VIII and IX* were taken at successive hours after the injection with blood pressure of 92, 90, 98 and 85 respectively. These experiments seem to show that the result is as good as can be hoped for with acacia.

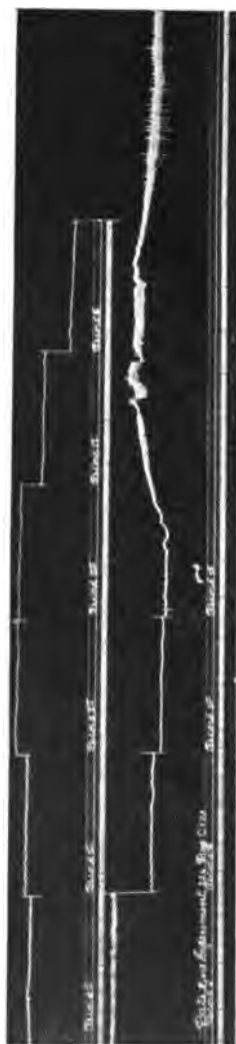


FIG. 483



FIG. 484.



FIG. 485.

FIG. 483.—Kymograph record showing the results of the injection of an alkaline acacia solution. *Record I*, normal blood pressure 148. *Record II*, after exposure of the abdominal viscera for one hour; blood pressure 88. *Record III*, after exposure of the abdominal viscera for two hours; blood pressure 75. *Record IV*, after replacing the viscera for ten minutes and the injection of 146 c.c. (20 c.c. per kg.) of a 7 per cent solution of acacia and 4 per cent solution sodium bicarbonate; the blood pressure increased to a maximum of 118. The succeeding records were taken at one-hour intervals after injection. The decrease in blood pressure occurring in the last record is characteristic of the action of an alkaline acacia solution, but usually blood pressure is not maintained for so long a time.

FIG. 484.—Kymograph record showing a failure of acacia solution followed by a success with gelatin solution (Hogan's). *Record I*, normal blood pressure 140. *Record II*, one and one-half hours after exposure of the abdominal viscera; blood pressure 82. *Record III*, thirty minutes after the replacing of the viscera; blood pressure 94; 104 c.c. (20 c.c. per kg.) of a 6 per cent solution of acacia in 0.9 per cent. sodium chlorid were injected (signal A-B). The injection may possibly have been made too rapidly; at any rate there was little improvement in blood pressure. *Record IV*, taken thirty-five minutes after the injection of acacia; blood pressure 70; 104 c.c. of gelatin solution (Hogan's) were injected at the same rate the acacia had been injected; blood pressure increased to 112. *Records V, VI, VII* and *VIII* were taken at succeeding hours after the last injection. The blood pressure was respectively 100, 112, 118, and 110. The gelatin produced a much better result than acacia.

FIG. 485.—Kymograph record showing the action of the citrated blood after a failure of acacia and modified acacia solution. *Record I*, normal blood pressure 112. *Record II*, after exposure of the abdominal viscera for one hour; blood pressure 52. *Record III*, after the replacing of the viscera for five minutes; 70 c.c. (20 c.c. per kg.) of a 6 per cent solution of acacia in 0.9 per cent sodium chlorid solution were injected (signal A-B). The blood pressure increased to a maximum of 80, but soon began to decrease and in thirty minutes it was 55. *Record IV*, taken forty minutes after *Record III*; blood pressure 50; 70 c.c. of a modified acacia solution (6 per cent acacia, 10 per cent glucose, 1 per cent sodium carbonate, 1 per cent sodium sulfate) were injected (signal C-D). The blood pressure increased to a maximum of 110, but soon began to decrease. *Record V*, taken forty minutes after *Record IV*; blood pressure 60. *Record VI*, taken one hour after the last injection; blood pressure 56; 70 c.c. of citrated blood were injected (signal E-F). The blood pressure increased to a maximum of 85. *Records VII, VIII, IX*, and *X* were taken at succeeding hours after the last injection. Note the beneficial action of blood.





FIG. 486.



FIG. 487.



FIG. 488.

FIG. 486.—Kymograph record showing the restoration and maintenance of blood pressure by the injection of blood after a failure of acacia solution. *Record I*, normal blood pressure 105. *Record II*, one hour after exposure of the abdominal viscera; blood pressure 70. *Record III*, immediately after the replacing of the viscera; blood pressure 40; 70 c.c. (20 c.c. per kg.) of a 6 per cent acacia solution in 0.9 per cent sodium chlorid solution were injected (signal A-B). The blood pressure increased to a maximum of 70, but within thirty minutes had decreased to 50. *Record IV*, taken fifty minutes after *Record III*; blood pressure 48; 70 c.c. citrated blood were injected (signal C-D). The blood pressure increased to a maximum of 86. *Records V, VI, and VII* were taken at succeeding hours after the last injection, with blood pressures of 88, 90, and 88, respectively.

FIG. 487.—Kymograph record showing the effect of injection of dextrin followed by gelatin solution. *Record I*, normal blood pressure 115. *Record II*, one hour after the exposure of the abdominal viscera; blood pressure 65. *Record III*, fifteen minutes after the replacing of the viscera; 150 c.c. (20 c.c. per kg.) of a 20 per cent dextrin solution were injected. The blood pressure increased to a maximum of 120, but soon decreased to 60. *Record IV*, taken one hour after *Record III*; blood pressure 58; 150 c.c. gelatin solution (Hogan's) were injected; blood pressure increased to a maximum of 82. The succeeding records were taken at one-hour intervals after injection. Note the slow recovery and the failure of blood pressure.

FIG. 488.—Kymograph record showing the results of the injection of dog serum. *Record I*, normal blood pressure 110. *Record II*, after exposure of the abdominal viscera for one hour; blood pressure 64. *Record III*, after the replacing of the viscera for fifteen minutes; 110 c.c. (20 c.c. per kg.) of dog serum were injected. The blood pressure was increased to a maximum of 110. The succeeding records, *Records IV to VIII*, were taken at one-hour intervals after injection. The serum restored blood pressure to normal and maintained it for five hours, until the experiment was interrupted.



Fig. 489.



Fig. 490.

FIG. 489.—Kymograph record showing the beneficial action of dog serum after a failure of normal salt solution. *Record I*, normal blood pressure of 112. *Record II*, after exposure of the abdominal viscera for one hour; blood pressure 75. *Record III*, after the viscera had been replaced for ten minutes; blood pressure 65; 156 c.c. (20 c.c. per kg.) of normal salt solution were injected (signal A-B). The blood pressure increased to a maximum of 85, but in fifteen minutes had decreased to 72. *Record IV*, an equal amount of dog serum was injected (signal C-D). Blood pressure increased to a maximum of 120. *Records V, VI VII, VIII, and IX*, were taken at succeeding hours after the injection, with blood pressures respectively of 105, 110, 120, 115 and 105.

FIG. 490.—Kymograph record showing the beneficial results of citrated blood after a failure of acacia. *Record I*, normal blood pressure 130. *Record II*, after exposure of the abdominal viscera for one hour; blood pressure 80. *Record III*, after the replacing of the viscera for fifteen minutes; blood pressure 70; 116 c.c. (20 c.c. per kg.) of a 6 per cent acacia solution in 0.9 per cent sodium chlorid solution were injected slowly (signal A-B). The blood pressure increased to a maximum of 90, but soon began to decrease. *Record IV*, taken thirty minutes after the injection was stopped. Blood pressure 60. *Record V*, taken one hour after the injection; blood pressure 70. *Record VI*, taken one and one-half hours after the injection; blood pressure 74; 116 c.c. of citrated blood were injected slowly (signal C-D). The blood pressure increased to a maximum of 110 and then decreased slightly after the injection was stopped. *Record VII*, taken thirty minutes after the injection was stopped; blood pressure 118. *Record VIII*, taken one and one-half hours after the injection; blood pressure 118. *Record IX*, taken two and one-half hours after the injection; blood pressure 112. *Record X*, taken four hours after the injection; blood pressure 98. The animal was used for another experiment.

*Special measures.*—The purpose of most of the many special measures which have been devised for treating shock is to increase blood pressure either by decreasing the vascular capacity or by aiding in the return of blood to the heart. Strapping the limb and increasing intra-abdominal pressure should be of benefit, inasmuch as such measures decrease the vascular capacity, but their value is difficult to demonstrate experimentally. Rebreathing has also been recommended; according to Porter, it increases the action of the respiratory pump and thus aids the return of blood to the heart by sucking it into the thorax. The rationale of rebreathing in treating shock from the chemical standpoint is an integral part of Henderson's acapnial theory. The value and limitation of rebreathing in surgery and anesthesia were first carefully studied by Gatch. In previous studies on rebreathing in shock I have shown that the process is similar in the normal and in the shocked animal but that no measurable benefit results; this was confirmed by the present series of experiments.

*Drugs.*—Drugs are usually employed in the treatment of shock for one of two purposes; first, either as a general stimulant, with particular reference to their action on the circulation and on the central nervous system (strychnin, camphorated oil, alcohol, etc.); and second, as vasomotor constrictors (epinephrin, pituitrin, etc.). Following the theory that shock is due to excessive vasoconstriction, the nitrites have been recommended for the purpose of decreasing vasoconstriction. Morphin is also recommended, mainly for its depressing action on the central nervous system.

Many investigations have been made with regard to the value of strychnin in the treatment of shock. Most investigators are agreed that the drug is of no value, although many surgeons, relying on their clinical experience, still use it in large doses<sup>9</sup>. In experimental shock it is impossible to observe any effect of strychnin in doses smaller than those necessary to produce definite convulsive movements. It is questionable whether even these large doses produce a beneficial action; in our experiments it could not be said that any of the so-called stimulants were of value.

The value of the use of vasoconstrictors in the treatment of shock is still an open question. In the first place, although the decreased blood pressure is of great importance in shock, it is not known whether or not its increase by means of vasomotor constrictors is in itself of much permanent benefit to the organism, and it would seem that they

might be of distinct harm by decreasing the fluid supply to the tissues. In the second place, none of the vasoconstrictor drugs produce a very prolonged effect. Epinephrin is the most popular of these drugs to be employed in shock. It easily restores the decreased blood pressure and by continuous injection the blood pressure can be maintained for a considerable length of time. As soon as the injections are stopped, however, the blood pressure sinks to its former level or usually lower. In our experiments pituitary extract produced a more prolonged action and seemed to be of somewhat greater benefit than epinephrin. Of course, repeated doses of the former cannot be employed as in the case of the latter drug. In general it may be said that experimentally the vasoconstrictor drugs produce little if any permanent benefit in the treatment of surgical shock although they might be employed clinically.

The nitrites produce their characteristic depression of blood pressure when it has been decreased by exposure of the abdominal viscera, but certainly no beneficial result has been observed from their use. Neither is the effect of morphin marked, but since it has been shown that the drug changes the regulations of blood volume, it should be studied more fully<sup>2</sup>.

*Attempts to restore fluid volume.*—It has been shown that a definite and marked loss of circulating fluid accompanies low blood pressure after the exposure of the abdominal viscera.<sup>18</sup> This also seems to be true in other forms of experimental shock.<sup>12</sup> In many clinical cases of surgical shock there is a loss of circulating fluid,<sup>4, 5</sup> and it seems logical to treat the condition by an attempt to restore the lost fluid to the circulation. A large number of artificial fluids have been devised for this purpose. We have investigated the use of most of these solutions under the standardized conditions mentioned.

We usually injected the fluids to be tested with a burette although in some instances a continuous injection machine was employed. The former method proved the most practical, although it was impossible accurately to control the rate of injection. The effect of the injection depends somewhat on the rate at which the solution enters the vein. In general it seemed that the best results were produced with a rate that was just a little less than the amount which produced cardiac disturbance. Better results were obtained when the temperature of the solution was below 37° rather than above.

In our experiments the use of blood gave far better results than the use of any other substances except blood serum. If blood pressure is

not decreased to less than one-half its initial value after exposure of the abdominal viscera, the intravenous injection of citrated blood in relatively large amounts, 20 c.c. per kg., will practically always restore and maintain it for many hours. As a rule, equally good results have not been secured with any of the artificial solutions. Blood frequently restored blood pressure after other solutions had failed. Homologous blood serum will produce practically the same results<sup>19</sup>.

Blood and blood serum show in many ways their superiority over all artificial solution. They do not raise blood pressure more than some of the other solutions and quite frequently the blood returns more slowly to normal than after the use of some artificial mediums, but, whereas in most instances in which artificial mediums are used blood pressure soon drops to the shock level or below, after the injection of blood or serum, the increase in pressure is usually maintained for many hours. In shock the injection of any solution brings about a return of sensibility requiring higher ether tensions. The degree of sensibility is more marked after the injection of blood or serum than after any one of the solutions.

Physiologic sodium chlorid solution is usually employed to restore lost fluid volume; this is the least valuable of the artificial fluids used if the blood pressure has been lowered in the manner employed by us. Hypertonic saline solutions have been recommended and in some of our experiments they produced a definite beneficial action but the increased blood pressure was never long maintained. None of the saline solutions alone will maintain blood pressure for more than a very short time even when it has been reduced to but slightly below normal by exposure of the abdominal viscera. The saline solutions will usually pass out of the vascular system almost as fast as they are run in.

The use of sodium carbonate and bicarbonate in hemorrhage and shock was experimentally investigated several years ago; their use clinically has been emphasized recently.

Howell seems to have been the first to study the effect of an alkaline salt in shock. He studied the effect of injection of sodium carbonate in a condition of shock produced by different methods. The beneficial results of such injections in the experimental conditions of low blood pressure which he had produced were due, he concluded, chiefly or entirely to a direct action on the heart. Dawson in continuing Howell's study investigated the effect of the injection of sodium

bicarbonate in a condition of low blood pressure produced by hemorrhage. He found that it produced better results than the sodium chlorid solution, and suggested that the bicarbonate solution be used in those cases of shock accompanied by hemorrhage. Seelig, Tierney and Rhodenbaugh obtained marked beneficial results by the injection of sodium carbonate in the condition of experimental shock, and concluded that the results were not due to the bulk of fluid injected, the hypertonicity or alkalinity of the fluid, or to the free carbon dioxide, but to the specific action of the salt on the heart muscle.

Cannon, in his study of shock in the front line trenches, found that there is a definite decrease in the alkalinity of the blood in cases of shock. The injection of sodium bicarbonate relieved this and produced very marked benefit. Patients on whom the surgeon refused to operate were tided over the critical period by the injection of either sodium carbonate or sodium bicarbonate which produced a rise in blood pressure and especially an increase in pulse pressure, thus making it possible to operate in a very short time.

In our experiments more lasting benefit was secured by the injection of sodium carbonate or sodium bicarbonate than by normal salt solution. Neither of the alkaline salts, however, completely restored blood pressure, nor was the increase long maintained.

Glucose has been suggested and used in postoperative treatment by several clinicians.<sup>3</sup> Erlanger and Woodyatt investigated its action in experimental shock and found it to be of some benefit. In our experiments the injection of such solutions was of definite value although rarely was there a complete restoration of blood pressure, nor was the increase long maintained. Glucose when added to some of the other artificial solutions seemed to enhance their value.

Hogan first recommended gelatin as a medium to restore lost fluid volume. His formula was used in several of our experiments and gave good results in some. In general it is as satisfactory as any of the artificial mediums. Great care should be taken, however, in its preservation, because it deteriorates very readily and may produce untoward results. It was very difficult to modify the gelatin solutions by the addition of other substances, and no modification was found to be as safe or to give better results than Hogan's original formula.

We have used acacia and its various modifications as recommended by Bayliss. The addition of acacia to a transfusion solution certainly



increases the power of that solution to restore and maintain blood pressure. The results following the use of acacia, however, were quite variable and sometimes disastrous. This variability of action seemed to depend on both the acacia and the condition of the animal. It is quite possible that the results of our use of acacia have not been so good as those which others report because our acacia was not the same.<sup>21</sup> We obtained the best we could, however, and I am quite sure the average surgeon who wishes to use it clinically would obtain no better. The alkaline acacia solution, when properly made by the addition of sodium carbonate or sodium bicarbonate, usually produced a better result than acacia alone, but it is difficult to prepare an alkaline acacia solution and more difficult to sterilize it and, on the whole, it did not seem to be a safe solution to use. Good results were produced by the addition of glucose to acacia.<sup>7</sup> The modified acacia solution, which gave the best results in our experiments, consisted of 6 per cent acacia, 10 per cent glucose and 1 per cent sodium sulfate.

Many other methods for restoring fluid volume besides those already mentioned were tried. The rapid injection of 35 per cent solution of cane sugar, as recommended by Guthrie, usually fully restored the blood pressure but it was not long maintained. In acute hemorrhage, however, it produces good results. Various strengths of dextrin solutions were used; they restored the blood pressure more satisfactorily than the other artificial solutions, but they failed to maintain it. A 1 per cent sodium sulfate solution produced fair results. It is interesting to note that distilled water gives better results in experimental shock with regard to blood pressure than do normal salt solutions. Crude preparations of hemoglobin from dog's blood produced good results and seem to warrant future study.

In summarizing the various methods employed to restore fluid volume it should be emphasized that, (1), in these experiments blood or blood serum produced by far the best results; (2), the colloidal solutions were the best artificial solutions used; (3), in general the gelatin solutions produced a more favorable action than the acacia solutions although some of the modifications of the acacia solutions produced as good or a better action than the gelatin; and (4), care must be exercised in the use of gelatin and acacia because dangerous reactions may be produced with either.

## SUMMARY

All the more important methods of treating under standard experimental conditions a state that exhibits the clinical signs of surgical shock which is produced by the exposure of the abdominal viscera of a dog, under a constant ether anesthesia, until blood pressure decreases to the desired level, were tested. The therapeutic measures were tested after the viscera had been replaced and after determining the curve of the blood pressure.

The treatment of shock is described under four headings:

1. *General measures.*—Heat, keeping the head down, etc. The value of the classical use of heat, as well as the effect of cold in helping to produce the condition, was corroborated experimentally.

2. *Special measures.*—Strapping the limbs, rebreathing, etc. Experimentally, rebreathing was not found to be of importance.

3. *The use of drugs.*—Stimulants, vasoconstrictors. None of the drugs usually employed in the treatment of shock were found to be very effective.

4. *The restoration of fluid volume.*—The best results in the treatment of experimental shock were obtained by the injection of fluid media. The data of the experiments justify the conclusion that none of the artificial solutions give such good results as the use of blood. The so-called colloidal solutions and their various modifications give better results than normal salt solution, but their potency is certainly not equal to blood or blood serum and occasionally they might be harmful.

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# THE RÔLE OF THE PATHOLOGIST IN THE PRACTICE OF MEDICINE\*

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The definition of pathology clearly states that pathology is the science of disease, its nature, and cause. Since pathology is a comparatively recently developed science its importance as a routine clinical diagnostic adjunct has only begun to be realized. In fact, the pathologist has been generally thought of by most clinicians as an interesting luxury—a corrector or confirmer of diagnoses after the patient is dead. This conception seems strange to pathologists who have conscientiously devoted their lives to training students and investigating intricate problems of disease. Some pathologists undoubtedly are in close relationship to patients, but the majority of pathologists throughout the world, for technical reasons, spend most of their time apart from patients and practical clinicians. Few are clinical consultants who have to do directly with living patients, and few general clinicians consider them worthy of the status of clinical consultant.

In the early history of medicine, clinicians knew all that was known of pathologic conditions and processes simply because little was known about them. As opportunities for increased knowledge of disease arose as a result of detailed postmortem examinations and other laboratory procedures connected with the study of disease, some one person was kept busy dealing with the material and technic associated with such opportunity. That person was known as the pathologist—the clinician dealt largely with histories, symptoms, signs, and treatment.

These are general facts concerning the functions of these two important members of the medical profession. Each is enlarging his functional efficiency; the clinician is studying pathologic conditions and processes and the pathologist is gradually but perhaps too slowly beginning to associate himself intimately with the patient and his clinical colleagues.

Scientific efficiency can only be obtained by one method, namely,

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that of having the clinician intimately associate himself with the work and judgment of the pathologist without doing detailed laboratory technic and the pathologist associate himself with the work and judgment of the clinician in his study of the patient without doing routine technical procedures for which the clinician is especially trained. Each of these specialists has more than he can do, but together they can readily do more for the patient and science than either one alone. This is cooperative specialism which reveals itself in the accompanying figures which represent the part played by a group of clinical and research pathologists working intimately with a group of clinicians. The statistics represent the laboratory reports made on 49,083 patients registered during the year 1918.

1. Metabolic rates determined.....	2,875
2. Gastric analyses made.....	9,560
3. Bacteriologic and serologic examinations:	
Sputum.....	1,989
Stools.....	2,488
Cultures (general).....	1,510
Smears (general).....	491
Vaccines.....	120
Wassermanns.....	21,994
Blood groupings.....	583
Skin tests.....	441
Special examinations.....	1,736
Stains for B. tuberculosis (urine).....	968
Positive tuberculosis sputum.....	299
Total number.....	32,619
4. Urine examinations:	
General.....	7,981
Functional.....	6,891
Twenty-four hour specimens.....	47,784
Ureteral specimens.....	3,591
Special examinations.....	193
General and functional.....	2,586
Total number.....	69,026
5. Blood examinations:	
Complete cell counts.....	2,337
White cell counts.....	939
Other tests (specials).....	722
Hemoglobin determinations.....	5,614
Incomplete counts.....	20,573
Coagulation and special examinations.....	538
Total number.....	30,723
6. Miscellaneous examinations.....	83
7. Autopsies.....	530
8. Electrocardiographic records.....	1,285
9. Fresh tissue examinations (living patients).....	11,147
Total number of pathologic reports.....	157,848

The last figure (157,848) represents the number of laboratory reports on 49,083 patients and not the number of laboratory examinations, for frequently each involves many examinations and tests.

The pathologist's reports represented by these figures have one or more of the following values to the patient and clinician:

1. The diagnosis of which there might be a clinical suspicion is confirmed, that is, the clinician suspects that an ulcer of the lip or stomach is malignant and the microscopic examination confirms the suspicion.

2. The diagnosis in which there is no clinical diagnostic suspicion is actually made, that is, the clinician obtains a history of a gastric lesion, which, on exploration appears to be an extensive carcinoma; microscopic examination reveals the gastric lymphatic glands to be inflammatory. The patient has a negative preoperative Wassermann reaction and the specimen after the resection for the obstructive mass reveals an inflammatory condition which turns out to be syphilitic, confirmed by a positive postoperative Wassermann reaction. The diagnosis and prognosis are considerably altered.

3. Accessory pathologic conditions are recognized; that is, the clinical diagnosis of myomas of the uterus is followed by subtotal hysterectomy and a carcinomatous growth is found in one of the horns of the uterus, or on removal of a large mammary cyst in a young woman a small carcinoma is discovered by the pathologist in the vicinity of the cyst. Such accessory findings alter the degree of operative intervention and change the prognosis.

4. The clinical diagnosis is corrected, that is, the clinician makes a diagnosis of, and the surgeon removes a sigmoid mass which the pathologist discovers is simply a sigmoid peridiverticulitis, or an ulcer of the lip is excised for epithelioma, and it is found to be a syphilitic ulcer, or the removal of an appendiceal fistula is begun and the pathologist, from the secretion, shows the presence of actinomyces. The last condition should alter the surgical procedure because the patient would undoubtedly still have a postoperative fistula.

5. The positive clinical diagnosis is confirmed, that is, the clinician makes a diagnosis of syphilis from the presence of a small scar on the prepuce; the patient gives no history of primary or secondary syphilitic lesions but admits the great possibility and the pathologist reports a positive Wassermann; or the clinician diagnoses an endocarditis and streptococci are found in the blood; or there is a chronic inflam-

matory condition of the urinary bladder with pus in the urine and the clinician makes a diagnosis of tuberculosis from the history and the presence of an old tuberculous focus in the lungs; the pathologist demonstrates the *Bacillus tuberculosis* in the catheterized uretera specimen, or a patient has a profuse hemorrhage from the uterus after menopause, and in the absence of a pelvic mass a diagnosis of malignancy is made, and the scrapings reveal a carcinomatous polyp.

6. The degree of the process of disease is determined, that is, the surgeon makes a gross diagnosis of carcinoma of the stomach and finds a nodule in the liver which he thinks is metastasis, in which case he probably would not resect the stomach. Sections from the nodule reveal an inflammatory condition which may or may not surround a gallstone that has become ulcerated in the liver substance. The degree or extent of the disease is determined and the surgeon is led to resect a portion of the stomach. In patients with pathologic kidneys the degree of function is determined by the phenosulphonephthalein and blood-urea tests.

7. The physical status of the patient preparatory to possible operation is determined, that is, "exophthalmic goiter" or hyperthyroidism is diagnosed. The metabolic rate is greatly above normal which indicates a poor surgical risk or it is slightly above normal and indicates a good surgical risk.

8. Aid in determining the extent of the operation is given, that is, a young woman presents herself with a nodule in the breast; it is locally removed (never incised) and submitted to microscopic examination. The extent of the operation necessarily depends on the report. A young patient has prolonged irregular uterine hemorrhage for which a reliable surgeon or clinician hesitates to advise hysterectomy. The uterus is curetted and the diagnosis of carcinoma is made, followed by hysterectomy.

9. Data are given for the preoperative, operative, and post-hospital prognosis, that is, a patient has a slowly developing enlargement of the tibia; there is an enlarged lymphatic gland in the groin. Repeated Wassermann tests are negative. The examination of the gland is of prognostic value. An operation for removal of gallstones, bladder stones, ureteral stones, hypertrophy of the prostate, or carcinoma of the uterus is required, but the examination of the blood reveals a low hemoglobin and the renal functional test reveals marked

anemia and renal insufficiency. The prognosis is somewhat dependent on these findings.

10. The cause of death in non-operative and operative cases is determined, that is, in medical or operative cases not previously diagnosed the necropsy frequently clears up the diagnosis.

11. The cause of death due to false operative judgment is determined, that is, patients are sometimes advised to have operations and they die because of the presence of other pathologic conditions which are recognized only at necropsy. Operative procedures sometimes lead surgeons to work with tissues, the vitality, or the character of which, is such that they will not survive the treatment. This has been seen rarely in resections in which the tissues were so disturbed by anemia, inflammatory reactions, or carcinoma that sutures did not functionate. The cause of the subsequent peritonitis is revealed at necropsy.

12. Faulty operative technical causes of death are determined, that is, unintentional ligation of ureters, or ligation of blood vessels necessary to intestinal blood supply, or improperly placed intestinal anastomosis causing death are revealed at necropsy.

13. Assistance is given in determining causes and methods of surgical infection, that is, routine bacteriologic examinations of operative wounds, operative materials, contents of organs operated on, or tissues lead to a better control over possible infections.

14. Assistance is given in clinical, surgical, and laboratory research.

These simple examples are but a few of many instances of the relationship of laboratory procedures and judgment to efficiency in the practice of medicine. In the series of patients under discussion each averaged 4.2 laboratory reports, each of which represents usually many examinations; of these 45 per cent were of necessity microscopic examinations. The data represent the relationship of the pathologist to general patients and may be supplemented by figures illustrative of the relationship of tissue pathology alone to diagnosis and surgical operations:

Twenty-two and seven tenths per cent of the 49,083 patients furnished diagnostic and surgical tissue specimens for examination, and 3.5 per cent had specimens of tissues removed solely for diagnostic purposes. Of the latter, 83 per cent were of necessity microscopic diagnoses.



In the series of patients operated on during the same period there were 11,149 tissue reports made, 16.7 per cent of which were of necessity microscopic examinations. This number varies from 15 per cent to 30 per cent in different series which have been studied from year to year. Of the last 14,167 operative cases in which microscopic examination, which is routinely made of all specimens, was necessary to diagnosis in 20 per cent.

In conclusion it may be stated that the statistics briefly presented here should be sufficient to show the medical profession that laboratory methods which were formerly considered principally of postmortem and research interest have become an essential part of the efficient routine practice of medicine.

## A MATHEMATICAL TERMINOLOGY FOR NEOPLASIA AND ITS SIGNIFICANCE\*

W. C. MACCARTY

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In 1918 I presented a biologic conception of neoplasia and indicated its relation to practical utilization of pathology in the practice of medicine and surgery. At that time neoplasms, as such, were not mentioned; it was believed that the first thing of importance was a clear understanding of a process of neoplasia within the body rather than the gross manifestations which have long been the object of rather crude consideration clothed in a terminology which differs in the hands of practically every accepted authority on pathology.

Neoplasms have been known to physicians and to the laity at least since the beginning of recorded medical history, although many pathologic conditions which are classified under the heading of tumors are now known not to be of true neoplastic character and do not belong to what we consider neoplastic diseases. Our real knowledge of tumors, and especially cancer, dates from the time of Hippocrates, but their cellular nature was not known until the time of Johannes Müller and Rudolf Virchow who described the condition and its many gross manifestations in a language which bears close resemblance to the language which appears in one of the last textbooks on the subject. Much has been written but little real knowledge has been added to that of fifty years ago. We still speak of adenocarcinoma, medullary carcinoma, scirrhous carcinoma, comedocarcinoma, colloid carcinoma, and cancer en cuirasse, and content ourselves with these. Modifications of terminology have been made, but none has been universally accepted because the bases of their formulation have always been speculative.

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The idea of conception that neoplasms have their inception in acquired or inherited rests still prevails not only in the minds of the profession at large but in the minds of expert pathologists. In the minds of some, neoplasia is a thing apart from cellular regeneration or hyperplasia; it represents some intrinsic cellular abnormality or some disturbance of body control over growth; in fact, to many it is vested in mystery, penetration of which must await some unusual discovery. As a matter of fact this discovery will probably be so simple, like most real discoveries, that we will wonder why it has been missed so long. At least the problem might well be approached in the light of known biologic facts. These facts have already been published and need only to be mentioned as a basis for a consideration of their practical application to neoplasia and to neoplasms in general.

It has been observed that nature provides for the regeneration of human tissues in two ways which might be called direct and indirect, the former consisting of division of specific tissue cells, and the latter of the division of reserve cells which are set aside for the purpose of regeneration of specific tissues by the process of multiplication, specialization, and differentiation. Direct regeneration of tissues represents the most primitive form of reproduction and doubtless occurs in the reproduction of endothelial tissues and perhaps some others, the reserve cells of which have not been seen. Indirect regeneration is seen in such specific tissues as those represented by squamous cells of the skin, secretory cells of the sebaceous, sweat, and mammary glands, fibrous connective tissue, lymphocytes, erythrocytes, osteocytes, chondrocytes, and glandular cells of the prostate, all of which specific tissues possess reserve cells which have been seen. During chronic destruction of these tissues the reserve cells react in a definite manner with a certain sequence characteristic of the behavior of living cells throughout nature. They become hypertrophic, hyperplastic, and migratory. In the light of biology these may be interpreted as hyperactivity against antagonistic things or forces; increase of mass action against such antagonists, and attempt at change of environment, all of which are defensive reactions and constitute the essential means of self-preservation. But we have not been accustomed to think of the human body except as a whole. We have not been sufficiently convinced of the principle of evolution to make us focus our attention on the actual facts pertaining to the development of our complex being from a single microscopic cell such as is the ovum. While we have realized that this cell contains the

potentiality of the complex human body, we have failed to appreciate and emphasize such phenomena as differentiation, specialization, and regeneration, which are coincident to development and preservation after development.

We have marvelled at and accepted the conception that following the segmentation of the ovum three layers of cells develop from which we have been content to give the origin of all of our tissues and dogmatically believe and teach that once a derivative of one of the layers always a derivative of the specific layer. This is a crude morphologic conception which had its inception in the infancy of embryology.

It is an heirloom difficult to throw aside in so far as its real significance is concerned. As a matter of fact the evolution of the many tissues of our body may be more accurately expressed by stating that all the different specific tissues arise from the single cell by the process of segmentation, differentiation, and specialization. Instead of saying that we have ectoblastic, mesoblastic, and endoblastic tissues and trying to identify each adult tissue with one of these, it might be more correct to state that from the ovum all of the different kinds of cells arise. Each tissue cell deserves a name; each must be regenerated during life or be so plentiful that partial destruction will not be fatally detrimental to the whole communism of which they are specialized and differentiated parts. These facts must be clearly appreciated before either neoplasia or its resultant neoplasms can be considered scientifically and described consistently and accurately. The three reactions (hypertrophy, hyperplasia, and migration), which have been shown to occur in eleven tissues of the human body, may be hypothetically applied to all of the known tissues, although some are so highly differentiated and specialized that they probably possess no means by which they may be regenerated. This is probably true of the parenchyma of the nervous system and perhaps of many if not of all of the so-called end-organs of this system. It may also be true of the muscles. Aside from these all our tissues are capable of regeneration either directly or indirectly, although the degree of regeneration varies for different tissues. The rate of regeneration for each tissue, however, must be determined experimentally at some future time.

The reactions may be diagrammatically expressed as follows:

DIAGRAM 1

	adeno-	
	audito-	
	cardiomyo-	
	chondro-	
	endothelio-	
	epithelio-	
	erythro-	
	fibro-	
	glio-	
	gusto-	
	leiomyo-	
	lenko-	
Primary (hypertrophy).....	lipo-	
Secondary (hyperplasia).....	lympho-	cytoplasia
Tertiary (migration).....	melano-	
	myo-	
	myxo-	
	neuro-	
	odoro-	
	perithelio-	
	pilo-	
	rhabdomyo-	
	sebo-	
	tactilo-	
	tendo-	
	visio-	
	etc.	

There are other factors which should be known in connection with the reactions. Thus the anatomic location of the reaction, gross manifestations, and the degree of cellular differentiation must be known in each case since these have something to do with the limits of the neoplastic process and hence give some idea of prognosis. They may be added to Diagram 1 in the following manner:

DIAGRAM 2

Location	Gross form	Biologic and clinical reaction	Tissue involved	Degree of differentiation
Capito- Collo- Cranio- Auriculo- Naso- Linguo- Labio- Laryngo- Etc.	circumscribed diffuse cystic extracystic ductal intraductal periductal papillary polypoid ulcerated	primary secondary tertiary	audito- adeno- cardiomyo- chondro- endothelio- epithelio- erythro- fascio- fibro- glio- gusto- leiomyo- leuko- lipo- lympho- melano- myo- myxo- neuro- odoro- osteo- perithelio- pilo- rhabdomyo- sebo- tactilo- tendo- visio- x-	cytoplasia with or without primary secondary tertiary

The terminology expressive of these facts may be abbreviated as follows:

DIAGRAM 3

Location	Gross form	Biologic and clinical reaction	Tissue involved	Degree of differentiation
Capito- Collo- Cranio- Auriculo- Naso- Linguo- Labio- Laryngo- Etc.	circumo- diffuso- cysto- extracysto- intracysto- ducto- intraducto- extraducto- papillo- polypo- ulcero-	primary secondary tertiary	audito- adeno- cardiomyo- chondro- endothelio- epithelio- erythro- fascio- glio- gusto- leiomyo- leuco- lipo- lympho- melano- myo- myxo- neuro- odoro- osteo- perithelio- pilo- rhabdomyo- sebo- tactilo- tendo- visio- x-	cytoplasmia { primary secondary tertiary

They may also be symbolically expressed as follows:

Location	Symbol	Biologic and clinical reaction	Tissue involved	Degree of differentiation
			Au	
			Ad	
			Cm	
			Ch	
			En	
			Ep	
			Er	
			Fa	
			Fi	
			Gl	
			Gu	
			Lm	
			Le	
Capito-	$\Delta$	primary secondary tertiary	Li	{ primary secondary tertiary
Collo-	$\Lambda$		Ly	
Cranio-	O		Me	
Auriculo-	$\Phi$		My	
Naso-	$\Theta$		Mx	
Linguo-	T		Ne	
Labio-	$\Pi$		Od	
Laryngo-	$\Psi$		Os	
Etc.	P		Pe	
	$\Omega$		Pi	
	Z		Rm	
			Se	
			Ta	
			Te	
			Vi	
			X	

This method of describing neoplasia is similar to that utilized by chemists to describe the structural factors in complex compounds. Like that of chemistry it serves the expert and is of little practical value in the daily use of compounds. Without them, however, the expert would be at a loss to convey his ideas to his fellow expert. The factors to be remembered in this biologic conception of neoplasia are, however, so few in comparison with those of chemistry that they can easily be mastered by every medical student. This would not require so great an effort as is now expended in attempting to master the terminology of neoplasms given in textbooks. If a student has recourse only to one textbook he may be happy, but when he comes in contact with other books or with students who have used other books he will soon find his terminology of neoplasms somewhat confused and hence



come to the conclusion that the pathology of neoplasms is far from being a mathematic or exact science. If the student has a knowledge of exact sciences such as mathematics, physics, and mechanics he will be subjected to keen disappointment early in his medical career. His former ideals of medicine as a science will doubtless fade away and leave him with nothing to cling to but the noble spirit which has been back of the practice of medicine in its feeble efforts to become scientific.

And now we must have some colloquial terminology for neoplasms which are the results of neoplasia. The physician and surgeon usually think of these and not of the process of neoplasia. Pathologists have likewise thought only of neoplasms, but in doing so they have given their practical colleagues a code of communication of ideas of them which is filled with synonyms, based on crude analogies to unrelated factors and which in no way describes anything but the grossest manifestations which were known a century, and perhaps centuries, ago. In so far as helping the physician and surgeon in his efforts to prevent, ameliorate, and cure the pangs produced by neoplasms he has failed to progress. He has merely kept alive the traditions of the ancient masters who did well within their means.

In so far as neoplastic cells are concerned they do certain things, that is they reproduce themselves, sometimes slowly, sometimes rapidly; they sometimes become rapidly differentiated\* into adult tissue cells for which they were originally intended as regenerative (textoblastic) cells; they sometimes become incompletely differentiated and simulate adult tissues in arrangement and cellular polarity without attaining the complete morphology of any adult tissue (these are frequent phenomena in many neoplasms); they sometimes remain absolutely undifferentiated and hence resemble in no degree any adult tissue.

As a result of these facts all neoplasms may be divided into three groups, *textomas*, *pseudo-textomas*, and *blastomas*.

*Textomas*† embrace all neoplasms composed of one or more completely differentiated tissue cells (textocytes). Such neoplasms may increase in size, but their growth is very slow as a result of the rapid, complete differentiation of cells into adult tissue cells. Such tumors produce detrimental effects by virtue of pressure, by which they may

\* By differentiation we mean in biology the structural or morphologic change coincident with special function.

† The term textoma is derived from "textus" meaning tissue and "oma" meaning tumor. Although this combination of Latin and Greek may seem inconsistent to linguistic purists such combinations have become common in science.

interfere with the natural functions of neighboring structures or may produce actual destruction of neighboring organs by the production of atrophy resulting from interference with local circulation.

Neoplasms, such as have been called "adenomas," "fibromas," "myomas," "chondromas," and "osteomas," if complete differentiation can be demonstrated, belong to this group. The main difficulty with utilizing such terms as fibromas, myomas, etc. arises from the fact that complete tissue differentiation has not been the only criterion for calling a tumor adenoma, fibroma, myoma, etc. Each of these has, heretofore in practice, represented also conditions of incomplete degrees of tissue differentiation, since the terms may easily include neoplasms somewhat resembling true textomas but proving to be pseudo-textomas on careful high power examination of cells. It must be remembered always that the regenerative cells of a textoma as well as the rest of the regenerative cells of the body may take on rapid growth and cause a textoma to become either a pseudo-testoma or a blastoma.

*Pseudo-textomas* embrace all of those neoplasms that are composed of cells which resemble but do not have complete adult morphology, in other words, composed of cells which have not reached the stage of complete differentiation. Many neoplasms present this condition, and the pathologist is very frequently unable absolutely to recognize the adult tissue which the cells of the neoplasm are apparently attempting to evolve. The cells of such a neoplasm as so-called adenocarcinoma or alveolar sarcoma may arrange themselves to form incomplete tubes or acini without the cells having the adult morphology of any cells of the body which are normally arranged into tubes or acini. This fact has frequently caused great difficulty in differentiating endotheliomas and adenocarcinomas, a differentiation which is probably only of academic or scientific interest and does not materially affect the patient, since there is no reason to make us believe that a neoplasm of endothelioblastic origin is any more or less malignant or benignant than one of adenoblastic origin.

Some pathologists seem to think, at least judging from impressions received from many, that there is a difference in malignancy between what they call an endothelioma and an adenocarcinoma, but there is considerable dispute about what they really call endothelioma, and this dispute has not been satisfactorily settled. Hence they may be incorrect in their generalizations. In my experience, when the cells of a neoplasm are so highly differentiated that I can definitely prove that the

neoplasm is an endothelioma, I can see no evidence of rapid growth. The same may be said to be true of any neoplasm composed of glandular cells. When such cells are so highly differentiated that I can positively state and prove that they are of a certain specific glandular type, then I see no evidence of rapid growth. In both cases I consider that I am merely dealing with neoplasms composed of adult tissues, and I immediately put them under the heading, textomas, and consider them as having the characteristics given under this heading.

From a clinical standpoint, pseudo-textomas are growing neoplasms which not only have the detrimental qualities of destroying by pressure that the textomas have but also have the power of direct invasion and metastasis by virtue of their undifferentiated and partially differentiated cells.

*Blastomas* embrace all neoplasms which are composed of cells which are undifferentiated, regardless of origin. In most cases the origin is indeterminable, and when it is determinable it is largely so from location alone. If one knows the normal tissues of an organ and finds all but one tissue perfectly differentiated, it might naturally be supposed that that one is taking part in the neoplastic process. This method of identification is largely one of exclusion, although one may sometimes obtain some suspicions from the size of the cells. If there are any morphologic characteristics which suggest a normal adult tissue, the neoplasm belongs to the group of pseudo-textomas.

These neoplasms are clinically malignant, and by virtue of their being composed of completely undifferentiated cells they are more primitive in type and, hence, are governed by the laws of cells rather than the laws of multicellular organizations. They are cytotypic and not textotypic. They therefore have a greater power of reproduction and migration and hence are more apt to be malignant.

In the second group (pseudo-textomas) great confusion has arisen in the older terminology by virtue of the fact that many pathologists have frequently attempted to state the exact tissue which the neoplastic cells resemble without being absolutely positive. Thus some pathologists call certain neoplasms endotheliomas, some carcinomas, some epitheliomas, and some sarcomas, when as a matter of fact the real nature cannot be absolutely established, and the establishment of the fact would make no special difference in the treatment or outcome in so far as the patient is concerned. Such disagreement on the part of

the pathologists merely serves to confuse the clinician and make his confidence in the pathologist somewhat disturbed.

If one can be absolutely certain of the tissue which is being structurally approached by the neoplastic cells, then one may add the root of the tissue name to the term pseudo-textoma. This is, however, of no great value to the clinician except perhaps to give some idea of the organ from which a metastatic neoplastic condition arose. In actual experience even this is not of very great importance because usually he already knows, or if he does not know the origin, he does know that he can do practically nothing for a patient with metastatic growths. But one may, if recognition of the tissue is absolutely possible, speak of adeno-fibro-myo-osteo-chondro, and so forth, pseudo-textomas.

In the third group (blastomas) which consists of neoplasms composed of undifferentiated cells, no denominating name can be attached.

The most important factor relative to neoplasms is their benignancy or malignancy. This factor is dependent on the rapidity of growth, the degree of cellular differentiation, encapsulation, locality of the growth, migration of the cells, and the natural defensive mechanism of the individual possessing the growth.

The last item is not sufficiently understood, but there are a few things, regarding which something is known, that is, lymphocytic infiltration, fibrosis, hyalinization, and calcification, all of which play a part in surrounding neoplastic cells in varying degrees in the order named. Perhaps in the early stages of neoplasia these general defensive reactions sometimes destroy neoplastic cells. This is, however, not known, although it seems possible in view of the fact that disintegrating neoplastic cells are frequently seen completely surrounded by one or some of these reactions. Despite them, however, fatal neoplasia occurs frequently. How much they impede the rate of growth remains to be shown.

The neoplastic conditions I have observed have been grouped according to the conception herewith presented, and this conception has served efficiently from a clinical as well as a biologic standpoint. I have been unable to conform experience to existing test-book terminology or the terminology to experience. From a practical as well as from a scientific standpoint it seems wise to divide the science of pathology in so far as neoplasia is concerned and perhaps other more exact

sciences into a science for the practitioner and one for the expert. We all know something about chemistry and utilize chemical compounds efficiently without knowing their exact chemical formulas which every expert chemist knows. We have names for these compounds and the names are associated with certain essential characteristics, and with these we work efficiently, but the expert must know the formula in order to understand many of the characteristics which it is not necessary for us to know in ordinary daily life. This in no way prohibits the practitioner from knowing the expert's conception and terminology. In fact he should be taught it just as he was taught detailed chemical terminology and formulas during his course of education.

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## THE PATHOLOGIC SERVICE OF THE AMERICAN EXPEDITIONARY FORCES\*

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*Introduction.* The technical work of the laboratory Section of the Division of Laboratories and Infectious Diseases was so modified by the stages of developmental organization and by the incidence of epidemics and hostilities, that it may be divided roughly into four periods:

1. From the landing of troops, June 10, 1917, to Nov. 30, 1917, about which time a large number of cases of pneumonia developed.

2. From Dec. 1, 1917, to May 31, 1918, when the hospitals of the A. E. F. began to be concerned most actively with wounded soldiers following the heavy German offensive of May 28.

3. From June 1, 1918, to Nov. 30, 1918, the period of serious epidemics and of greatest battle activity, during which time the laboratory was concerned largely with cases of enteric disease, influenza, and with recently wounded patients.

4. The period of demobilization from Dec. 1, 1918, to May 15, 1919.

The first period, from June 10, 1917, to Nov. 30, 1917, was one of tentative organization in which the laboratory staffs were for the most part doing the clinical pathology incident to ordinary illness and accidents in a small body of troops in the S. O. S. or in training. The Wassermann service was begun in September, 1917. In the few laboratories then operating ( 4 camp hospitals, 8 base hospitals and 2 section laboratories) a small but important autopsy service was begun. Very meager data concerning the technical laboratory work of this period are available since no monthly reports were made.

In the second period, from Dec. 1, 1917, to May 31, 1918, laboratories in twelve more camp hospitals, three evacuation hospitals,

\* Abstract of chapter written for the History of the Medical Department of the United States Army.

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ten more base hospitals and the Central Medical Department Laboratory, began to function, and the organization of the Division of Laboratories and Infectious Diseases was perfected, thus greatly increasing the facilities for all types of technical work. Early in this period epidemics of pneumonia, diphtheria, scarlet fever, and meningitis taxed these facilities to their full capacity for routine clinical and bacteriologic examinations. At the end of this period the system of monthly laboratory reports was begun, but the available information for most of the period is quite incomplete.

The beginning of the third period was marked by the German offensive, May 28, 1918, in the Chateau Thierry district, which brought large numbers of American wounded into the hospitals. The Medical Department, on the laboratory side as well as on the administrative, clinical, and surgical sides, was then still greatly undermanned. So great was the need for medical attention that in many instances all laboratory officers were diverted from laboratory work to the more direct care of the wounded. At no period from this time on until the signing of the armistice were there half enough laboratory officers at work in the laboratories to make the necessary routine technical examinations, while research was wholly out of the question. However, by working without regard to fatigue or the day's length, as did their fellows in the medical and surgical divisions, they succeeded, besides helping out the other divisions, in organizing and developing their laboratories, in doing most of the absolutely essential clinico-pathologic routine work, and in meeting emergencies such as making large numbers of bacteriologic examinations and autopsies incident to battle casualties and epidemics of enteric diseases, influenza, diphtheria, meningitis, and so forth. This was accomplished in most instances, except for certain 8-chest transportable outfits obtained in England, with equipment so inadequate as to have been considered utterly impossible under peace conditions. If the amount and character of work done during this third period is studied and the meager personnel and equipment is considered, only astonishment is elicited at what was accomplished. By November 1 the total number of laboratories in operation had risen to nearly 300, the personnel was advantageously distributed, officers had learned really to "make bricks without straw," a fine esprit du corps had developed, and, had the war lasted a few months longer, the magnificent team work would have triumphed over every obstacle and resulted in the greatest



system of laboratories that the world has ever seen. This third period of the laboratory activities of the A. E. F., that is from June 1, 1918, to Nov. 30, 1918, will forever stand as a monument to the ability of the American laboratory man to get results regardless of conditions.

The available information concerning the technical work for this period is fairly good. In May, 1918, a standard form (No. 5) for laboratory reports to the Director of the Division was produced and beginning with June, 1918, this report was received monthly from almost all laboratories in operation in the A. E. F. This form, which was intended primarily to supplement personal inspection from the office of the Director of the Division, presented sufficient clinical information concerning the activities of each hospital to enable the reviewer of the report to determine something of the character and amount of work which should have been done by the laboratory and the personnel available for its accomplishment. The laboratory activities were divided into six groups as they were ordinarily distributed, when distribution was warranted, among the personnel of the laboratory. All attempts to determine the clinical incidence, as of infectious diseases, were purposely omitted from the report since it was believed that these more properly belonged to Special Reports of the Section of Infectious Diseases. The number of "positive" examinations in certain diseases was given merely to aid the reviewer in determining whether the clinician was under-using or over-using the laboratory. The careful review of each report immediately upon its receipt and, if necessary, the return of a critical indorsement thereon was tedious labor but did much to improve the weak points in the service.

The signing of the armistice marked the beginning of the fourth period of the laboratory service and, regrettably in some respects, the period of its dissolution. Many laboratory officers in civil life, unlike their fellows in clinical medicine and surgery, had not been enjoying large incomes and had left their families inadequately provided for. Many of them were dependent on teaching and hospital positions which are filled at stated periods and which cannot be resumed at any time of year as may a private practice. Many laboratory officers requested leave to return with their hospital organizations, a request which could not well be refused though the laboratory personnel was still far below that of any other medical service. At the same time typhoid fever

made its appearance in a number of organizations, rendering necessary extensive bacteriologic examinations. Troops in training areas were being very thoroughly examined for venereal diseases, and the concentration of troops at embarkation camps and base ports resulted in potential danger points which demanded a very great increase of laboratory service. Thus, as a result on the one hand of decreased personnel and on the other of increased service demanded, much of the technical service of the laboratory division even in this final period was done under considerable stress. Fortunately, however, early in this period the arrival and distribution of laboratory supplies had been greatly expedited which, coupled with the transfer of material from organizations being demobilized, greatly improved the physical conditions under which the work was done.

*Clinical pathology.*—In the field of clinical pathology the laboratory officer by urinalyses, blood cell counts, and so forth assists the attending medical officer and surgeon by furnishing information, which aids in determining the physical condition of the patient. In the examination of feces for parasites and ova, blood for malarial parasites, sputum for tuberculosis bacilli, spinal fluid for meningococci, preparations from venereal lesions for gonococci or treponemas, and so forth, his work is final if his findings are positive. But in all of these studies he stands in the relationship of consultant to the attending medical officer or surgeon and is dependent upon them for the receipt of specimens and for notification of their need of his services. Hence the amount of clinico-pathologic work done in a hospital which is properly manned and equipped depends very largely upon the hospital clinicians. Not all hospitals in the A. E. F. were manned by such officers well trained in the selection of cases in which clinico-pathologic examinations might be of assistance; nor were they all sufficiently trained in interpreting the results once they were obtained. In some instances serious diagnostic errors were made which might have been prevented by even a urinalysis; in others the laboratory was called upon to make large numbers of difficult examinations in the search for the specific cause of a disease which was scarcely even suggested by the symptoms. Personal supervision by medical and surgical consultants did much to improve the clinical services in this respect but were obviously inadequate to cover with sufficient detail the field of nearly 300 hospitals. It is believed that commanding officers of hospitals might well give more attention to the preservation of

the proper balance between their several professional services. In hospital centers the placing of the laboratory officer of the center on the headquarters staff greatly increased the efficiency of the laboratory service of the center and made for the better coordination of the laboratory work with that of the other professional services.

The clinico-pathologic service of the first period up to Nov. 30, 1917, constituted the bulk of all laboratory work, though it was far from large. During this period, the number of patients in hospital was small, since the troops were mostly in the S.O.S. or in training areas, and clinicians were thus able to study their cases carefully and to utilize the laboratory facilities to good advantage. Many of the patients in hospital during this period were suffering from acute infectious diseases of respiratory origin, though true pneumonias did not reach a high rate until December. A very high venereal rate occurred in November, 1917, making necessary many routine laboratory examinations in this field. The laboratory records for this period, however, are very meager since regular monthly reports were not made.

The clinico-pathologic work for the second period, from Dec. 1, 1917, to May 31, 1918, was similar to that of the first period. The epidemic of pneumonia, starting in the fall of 1917, gradually subsided, but a relatively large number of patients with other diseases, particularly meningitis, scarlet fever, diphtheria, and measles, were hospitalized and on these a large amount of clinico-pathologic work of a routine character was necessary. The relatively high venereal rate in December, 1917, dropped materially toward the end of the second period.

The total amount of clinico-pathologic work done during the first and second periods was low in relation to the number of cases in hospital and to the number of both commissioned and enlisted personnel. This was due to obstacles in housing, lack of equipment, untrained enlisted personnel, and in some instances to "overtrained" commissioned personnel. Many of the first base hospitals in the A. E. F. were manned on the laboratory side as well as in the other professional departments by highly trained specialists. Many of these had been concerned in their recent civil experience only with teaching or research and it required a considerable period for some of them to readjust their ideals so as properly to evaluate simple routine clinico-pathologic examinations, as of urine and blood.

For the third period, from June 1, 1918, to Nov. 30, 1918.

the records are fairly complete though during this period the laboratory service, being undermanned to the extent of only about 40 per cent of its normal strength, was so greatly overworked as to make the keeping of detailed records very difficult.

During the fourth period, from Dec. 1, 1918, to May 15, 1919, though as already pointed out there was at first slight but soon a marked decrease in trained laboratory personnel, the continuance of influenza and the outbreak of numerous small epidemics of typhoid fever as well as the more careful venereal survey of all troops, made necessary a large amount of laboratory work.

Leukocyte counts showed a gradual increase monthly which failed to rise with the greatly increased number of patients in hospital and did not reach even an approximately proper proportion until February, 1919. This was most noticeable in the relatively small number of differential counts made and was probably due to failure of clinical officers to appreciate the importance of this diagnostic procedure, or their failure to insist upon the necessity for such counts.

Examinations for malaria which reached their highest number in August, 1918, were notable for their rarity though they probably covered the necessary field more completely than any other laboratory procedure.

Examinations of feces for parasites and ova and for entameba were altogether too few. There was little time for these during periods of great stress, but during the fourth period they might have been more generally done. It is unfortunately true, however, that laboratory personnel properly trained in the technic of these examinations was seriously lacking in the A. E. F. This defect is probably directly chargeable to lack of sufficient training in the subject in the medical schools of the United States.

Urine examinations were fairly numerous but their distribution and quality were very irregular. In many hospitals the specimens were intelligently selected, properly collected, and carefully examined. In some this was not true. In others very few examinations were made. Because of their number no variety of laboratory examinations are so likely to degenerate in quality through relaxation of vigilance at some step in the process as are urine examinations.

In examinations of sputum for tuberculosis bacilli similar relaxation is apt also to occur. Specimens which the laboratory officer knows are not intelligently selected or collected are apt to be superficially

examined, thus rendering negative reports of little value. In some hospitals as many as 400 or 500 specimens were examined with only four to five positives reported. It is true that these were intended as controls in cases of recovery from influenza and pneumonia, but it is feared that in many instances the lack of care in the collection of sputum and the lack of persistence in search for the bacilli, due to haste, made the negative findings of relatively little value.

The examination of gastric contents had a relatively small place as compared with such examinations in a large civil practice. Most of the individuals being young adults subject only to wounds and acute diseases, there was little necessity for the examination of gastric contents for the diagnosis of gastric ulcer or cancer. In addition, the x-ray was greatly depended upon in most suspected cases.

The occurrence of sporadic cases of true epidemic meningitis at widely separated points in the A. E. F. kept the whole medical department on the qui vive. While it cannot be demonstrated beyond peradventure that had no measures been taken serious epidemics of meningitis would have developed, yet it is probable that the early accurate diagnosis and the vigorous methods instituted in most instances immediately on the development of a single case served in large measure to prevent epidemics, since it is scarcely conceivable that of all the sporadic cases developing none would have been of sufficient virulence to have caused infection of contacts. In this service the laboratory officer rendered inestimable assistance to the attending medical officer.

Smears for gonococci showed a gradual monthly increase though not reaching a fair proportion until February, 1919.

Dark field examinations for *T. pallidum* were considerably, though not sufficiently, increased after the armistice. It was difficult to find enough officers to make the large number of necessary dark field examinations in a competent manner.

Except in the few instances noted above, the general quality of the clinico-pathologic examinations was good. A large number of clinicians had been trained in civil practice to expect and to interpret these examinations more or less intelligently. This counteracted the tendency on the part of some laboratory officers to turn this work over to untrained personnel. Just why macroscopic biologic diagnosis should be considered so much more abstruse—and therefore so much more worthy the attention of the laboratory officer than microscopic

diagnoses, for example of entameba or *T. pallidum*—is not apparent. Such was too often the feeling however. Medical schools might well give more thorough training in the use of the microscope, especially in the study of *T. pallidum* in dark field preparations, of entameba, and of intestinal parasites and ova. Fortunately in the A. E. F. during the period of greatest stress there was no necessity for any large number of any of these types of examinations.

A brief comparison of the number of clinicopathologic examinations with the total number of all examinations month to month and in the different types of hospitals may be significant in the apportionment of equipment and personnel for the various types of laboratories in future expeditionary forces:

In the headquarters laboratory and base laboratories of the S.O.S. sections the number of clinico-pathologic examinations totaled 22 per cent of the total number of all examinations in those laboratories. This varied slightly from month to month but the general average may be taken as an indicator of the relative amount of clinicopathologic examinations which was increased as previously pointed out by the fact that most of these central laboratories were associated with and doing clinical laboratory work for base or camp hospitals.

In base hospital centers and base hospital laboratories after the preliminary period of organization the percentage of clinicopathologic examinations settled down to a little more than 50 (average 53 per cent). This is probably a fair estimate for future similar organizations.

In camp hospital laboratories the percentage of clinicopathologic examinations averaged slightly higher than in base hospital laboratories. It is believed that this percentage would have been very materially higher had not camp hospitals, in a number of instances, functioned as base hospitals.

The greatest variation from month to month in the percentage of clinicopathologic examinations occurred in evacuation and mobile hospitals and averaged 55 per cent of the total examinations. This variation was due to the different conditions of "peace" and "combat" under which these organizations operated. Since in future expeditions it will be equally difficult to forecast the activities of these organizations, it would seem desirable that they be furnished with both personnel and equipment equal to any emergency.

In divisional laboratories the percentage of clinicopathologic examinations was fairly even from month to month, averaging 49 per

cent. It should not be forgotten, however, that the individual divisional laboratories varied greatly from month to month in their activities, some of them failing to function at all for several weeks at a time.

The total number of all clinicopathologic examinations for all laboratories was 51 per cent of the total number of all examinations for all laboratories. This percentage varied from month to month, being slightly less during periods of battle activity and of epidemics of acute infectious diseases owing to the increased necessity for bacteriologic diagnoses. Thus it would appear that equipment and personnel should be provided for future organizations under similar conditions sufficient to perform about 50 per cent as many clinico-pathologic examinations as of all examinations. It should be possible, however, to vary the type of examination at least 20 per cent in either direction. The limitation of equipment and the tendency to specialize the training of personnel along too narrow lines are both to be deplored. Emergencies must be met and both equipment and personnel adaptable to emergencies should be provided.

*Pathologic anatomy.*—At first thought pathologic anatomy would seem to have relatively little place in a military expeditionary force in which the laboratory's chief concern is in the control of infectious diseases and infected wounds. As it turned out, however, the unusual problems of diagnosis and treatment met with in the A. E. F. made work in pathologic anatomy one of the most important functions of the Section of Laboratories, and one of the most difficult to fill. The work may best be reviewed under the reported items of the macroscopic examination of operation specimens, histopathologic examination, and the making of autopsies.

In some laboratories the routine examination of material from surgical operations by the pathologists was an established practice, particularly after December, 1918. In many hospitals, however, this was neglected. This arose from two conditions; first, in civil life many surgeons had not previously learned the importance of the review of operative material by a pathologist for obtaining information which might be of value in the subsequent treatment of other cases or in the treatment of the same case; and second, during times of great battle activity the operating room attendants were too busy even to transfer the specimen and necessary data to the laboratory. Commanding officers of hospital organizations should realize the im-

portance of having all operative material reviewed by a competent pathologist as a routine procedure and not just occasionally on request of the surgeon. This laboratory service is inspectorial in character and should be so considered.

Histopathologic examinations, requiring as they do considerable time and experience in their preparation, were made with great infrequency during periods of epidemics and of battle activity when hospitals were crowded and laboratory personnel overworked. After the subsidence of the influenza epidemic and the cessation of hostilities a number of hospital organizations began the histologic examination of tissues which had already been collected. As a routine procedure, the chief field for section study in military laboratories under conditions of warfare would seem to be the control of gross observations on operative material and autopsy specimens. If it were possible to provide carbon dioxid for the making of frozen sections more of this work, particularly in the preliminary survey of operation and autopsy material, could be done than by the use of paraffin. However, since paraffin sections are necessary for examinations involving observations on bacteria, it would seem wiser to provide paraffin equipment as standard and frozen section or celloidin equipment only to meet special conditions.

A study of the distribution of the autopsy service by periods and in the several types of hospitals in the A. E. F. shows the following:

During the first period, to Nov. 30, 1917, very few postmortems were made in the A. E. F. The clinical service was extremely light, the attending medical officers and surgeons had time to study their cases with great care and thus, even of the few patients who did die, the necessity for a postmortem examination had not pressed itself on the attention of the attending officers. Of the postmortems that were made, either incomplete records were kept or those that were kept were in some instances lost, so that there remain for the period but fourteen protocols in all which have been received in the Office of the Director of the Division of Laboratories. Most of these autopsies were made at Army Laboratory No. 1, Naval Base Hospital No. 1, and Camp Hospital No. 33. These autopsies represent less than twenty-five per cent of the deaths which occurred during the period.

During the second period, Dec. 1, 1917, to May 31, 1918, though the conditions for the leisurely study of patients by clinicians,



and surgeons continued, the latter had come to realize their difficulties in diagnosis and treatment, and pathologists themselves had begun to take more interest in their work; thus autopsies increased in May to 57 per cent of the total number of deaths in the hospital. The percentage increase in April and May was further due to the fact that April 2 Circular No. 17, was issued from the Chief Surgeon's office, the first paragraph of which read as follows:

"Autopsies are authorized in all cases of officers and soldiers and should be performed whenever possible. These autopsies shall be performed only by Medical Officers or authorized assistants. At the conclusion of the autopsy the body must be restored, as far as possible, to its original form."

Though by the end of May, 1918, there were in the A. E. F. 72 hospitals and laboratories, there were less than fifteen pathologists capable of making postmortems and intelligently interpreting the results. This condition was due in part to the long neglect of autopsies in many civil institutions in the United States with the inevitable reduction in the number of pathologists, and in part to the overshadowing status of bacteriology in military laboratories. The autopsy service in the Army in the United States had not been established as a routine procedure, but on the contrary autopsies were made only on the written authority of the Commanding Officer of the hospital. However in the A. E. F. the need of a routine autopsy service, amounting in fact to professional inspection of the diagnostic and therapeutic measures of medical and surgical officers, became rapidly apparent during the summer of 1918. Surgeons were called upon to diagnose and treat, with little time for study or reflection, many gunshot wounds with the like of which they had had little or no previous experience. Even those who were well grounded in the general principles of surgery were forced to make decisions and institute treatment thereon without sufficient basis or study. As a result, there were errors in diagnosis and errors in treatment. The worst of these could be determined only by the pathologist. In like manner, attending medical officers, for example in cases of war gas poisoning and especially in the widespread epidemic of influenza and pneumonia, were brought face to face with conditions with which they were totally unfamiliar, and were frequently forced to make diagnosis and institute treatment with a very meager knowledge of the facts. Here autopsies were of tremendous importance in securing for the attending man a knowledge of the

pathologic lesions which knowledge he could use in the diagnosis and treatment of subsequent cases. When, late in the fall of 1918 and the winter of 1919, numerous isolated epidemics of typhoid fever in vaccinated troops began to appear, the conditions were in many instances so obscure that the clinicians failed to make the diagnoses, the pathologist being the first to recognize the true nature of the disease when the patient came to the autopsy table.

Looking forward to some such possibility as occurred, the Director of the Division of Laboratories, in June, 1918 requested that ten competent pathologists be cabled for from the United States in addition to those coming over with hospital organizations. These arrived in due time, and being placed advantageously, assisted materially in improving the service. In addition the activities in forward areas were covered to better advantage by dividing the territory into sectors and placing at Baccarat, Toul, Souilly, and Paris respectively, competent pathologists attached to an evacuation or base hospital therein, with orders to act as consultants for the surrounding areas. In addition to these measures, the importance of autopsies was brought to the attention of laboratory officers and commanding officers of hospital organizations personally by inspectors from the Office of the Director of the Division of Laboratories, by letters, and by indorsements on monthly reports. As a result, the autopsy service rapidly mounted and, though there were never enough competent pathologists in the A. E. F. to cover the needs at all points, there being only about 200 pathologists out of 685 laboratory medical officers at the time of the signing of the armistice, the service mounted in August and September of 1918 to 92 per cent of all deaths in hospital. In October the total number of autopsies reached 3,896 though this was but 85 per cent of the deaths in hospital, the autopsy service like every other being overwhelmed by the enormous number of deaths from influenza and the battle casualties of the Argonne offensive.

The distribution of autopsies among hospitals of the various types indicated where the stress for autopsy service came during the influenza epidemic and during battle activity. The greatest mortality was of course in the base hospitals. It is worthy of note that after July, 1918, many more autopsies were done in camp hospitals than in evacuation and mobile hospitals. This was owing to the greater number of camp hospitals and to the fact that many of them actually functioned as base hospitals. The lesson to be drawn from this expe-

rience is that competent pathologists should be provided for these organizations as well as for base, evacuation and mobile hospitals. On the other hand, it is doubtful whether conditions will ever warrant the performance of any considerable number of autopsies in field hospitals by personnel attached permanently thereto. Here it is believed the necessary study of battle casualties, particularly of gas poisoning, can best be done, as in the French Service, by centrally located laboratory officers provided with motor transportation for the rapid concentration at any point where gas casualties have occurred. This plan was attempted in the A. E. F. but for the most part failed for lack of transportation.

The general quality of the autopsies, in so far as their main object was concerned, namely obtaining data for the immediate information of the attending physician and surgeon, was very high. This is especially true when it is remembered that under the unusual conditions under which both physician and surgeon were working neither had any time to consider minute details of questionable importance. On the other hand, there were so many gross errors both in diagnosis and treatment which were of such unquestionably vital importance in the care of the sick and wounded subsequently coming under observation, that in many instances it required only the opening of the body to enable the merest tyro in morbid anatomy to demonstrate them to the attending medical officer. In most instances the attending physician or surgeon was keenly alive to the benefit to the case of tomorrow to be derived from these observations. Now and then a cock-sure physician or surgeon ignored the findings of the pathologist until it became necessary to force them upon him. Here and there the commanding officer of a hospital, usually in a forward area under the stress of a huge inflow of battle casualties, failed to recognize the importance of the pathologist's inspection of the other professional services, and placed his laboratory officer in charge of supplies or the mess, to the serious detriment of the diagnosis and treatment of the sick and wounded. There can be no question but that the uncontrolled surgery under such circumstances did great harm which might have been obviated had the pathologist been permitted to exercise his proper functions and point out to the surgeon the gross blunders the latter was repeatedly making.

Judged from the standpoint of records for subsequent scientific study the autopsy service was of very varied character. Only a rela-

tively small proportion of laboratory officers had had an adequate preparation in the interpretation of lesions at the postmortem table and, of these, still fewer had been properly trained in accurately recording their observations. Trained clerical assistants and typewriters were almost unobtainable. The records of some of the very good men are exceedingly meager. In times of great stress this was true of everyone's. Even one of the best pathologists, who made twenty-two postmortems in one day, of course left records of only the most essential facts. The incidence of tuberculosis other than as a cause of death was routinely recorded by but five pathologists who made any considerable number of autopsies. But as one goes through the 15,000 protocols which have been received in the Office of the Director of the Division of Laboratories and remembers the conditions under which most of the pathologists worked for a large portion of the busiest time, one is struck with the high quality of the work from a large number of the officers, many of whom previously had very meager autopsy experience. The officers in charge of the analyses of these protocols say they are convinced the quality of the records will compare most favorably with any consecutive series of similar size from any civil hospital or hospitals in the United States. This is of course due in part to the relatively narrow limits of age, sex, time, and disease variation.

Early in July the recording and cross indexing of autopsy protocols was begun in the Office of the Director of the Division of Laboratories. Inadequate assistance rendered progress in this direction very slow, however. After the signing of the Armistice, the release from duty elsewhere of a few competent pathologists made it possible to place the analyses of the autopsy protocols concerning a few diseases on a better basis. In order to facilitate the work in the Central Office and to obtain the benefit of the review by the competent pathologists scattered throughout the A. E. F., three office letters concerning respectively influenza and pneumonia, gunshot injuries, and war gas poisoning, were sent out to laboratory officers selected because of their ability and experience. These office letters gave forms for the analysis by the laboratory officer of all cases coming to autopsy under his individual observation. On the receipt of these analyses in the Office of the Director, they were compiled and coordinated with each other and with scattered protocols from other laboratories. Two other compilations are in progress, one on typhoid fever and another

on tuberculosis. It is believed that all of these will be of immediate military value. In addition to these, however, the other autopsy protocols contain a great wealth of data for subsequent study, for example, of meningitis, dysenteries, cardio-vascular lesions, and so forth.

One field of postmortem examinations which might have yielded invaluable results from the purely military standpoint was entered by but one pathologist in the A. E. F. This was the examination of the bodies of soldiers killed in battle. This service does not necessitate the making of autopsies but only a study of the site and character of immediately fatal injuries by competent medical officers with a good knowledge of anatomy and some appreciation of the character and effects of missiles. Where conditions will permit, a careful investigation of the battle dead in all of the different types of combat activity should yield information of inestimable value in both offensive and defensive warfare. The effectiveness or ineffectiveness of the many types of small arms missiles alone has been made the subject of but very little investigation with human targets under battle conditions. Until such a study can be made extensively and the observations collected and analyzed the relative effectiveness of offensive warfare with small arms, hand grenades, shell fire, poison gasses, and so forth, rests upon very incomplete and inaccurate observations and must remain largely a matter of conjecture. Similarly, without such studies, all attempts at the provision of armor which avoids on the one hand, unnecessary weight and extent, and, on the other, penetrability, are proceeding without what would seem to be absolutely essential information of combat results. Such information could readily be obtained during battle activity by temporarily attaching competent medical officers to burial parties.

*Plans for the future.*—In the future provision for clinico-pathologic work in laboratories in a military expeditionary force, there can be no question but that hospital and division laboratories of all types should be furnished with equipment and personnel for taking care of all clinico-pathologic work of the character indicated in the monthly report form, with the possible exception of dark field illumination apparatus for the study of venereal preparations. Whether, on the other hand, this type of work should cover the entire laboratory activities of any type of hospital in the next military expeditionary force is doubtful. The laboratory officer must have enough daily experience

to keep him trained for all emergencies which are apt to arise and it is doubtful whether any hospital which is apt to keep patients more than two or three days should lack the facilities for cultural bacteriologic examinations. Certainly each hospital should have at least one medical officer capable of making an intelligent postmortem examination.

In plans for the autopsy service in the future the general principle should be followed that whenever men die after having been made the subject of diagnosis or treatment, their bodies should be examined postmortem by competent pathologists. This policy of inspection of the services of the medical and surgical departments will furnish the greatest possible safeguard for the thoroughness and accuracy of their work. Of course such a policy presupposes a large number of well trained pathologists, and there is no way for men to obtain such training except by more general autopsy examinations in civil hospitals. Provision should also be made for the better correlation of pathologic work with that of the clinical services both in civil practice and under military conditions. Only by the most perfect liaison between these services can the sick and wounded receive proper diagnosis and treatment.

## MUSEUM AND ART SERVICE OF THE AMERICAN EXPEDITIONARY FORCES\*

L. B. WILSON

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In January, 1918, the Surgeon General requested authorization from the Commanding General A. E. F. to send a National Army Medical Museum Unit to France with the writer named as director. After receipt of the authorization, and after a delay of two months in planning for the collection of museum material in the camps and cantonments of the United States, the writer was ordered first to England to study the collections and methods of collecting by the British and colonial armies, and then to France for duty. In the meantime Circular No. 17 had been issued by the Chief Surgeon of the A. E. F. calling attention to the importance of collecting museum specimens and giving brief directions for their preservation.

The collection of museum and art material in France was placed under the direction of the Division of Laboratories. It was early apparent that the collection of pathologic material would be wholly dependent on the pathologists who would be making postmortems. The first task, therefore, was to assist in building up the necropsy service in the A. E. F., which at that time was very inadequate owing to lack of personnel. The need of a routine necropsy service in the A. E. F., serving as professional inspection of the diagnostic and therapeutic measures of the medical officers, became rapidly apparent during the summer of 1918. This inspectorial need was filled in a satisfactory manner, and although at no time were there enough pathologists to permit them to give more than incidental attention to the collection and preservation of pathologic material, on the whole the results were better than might have been hoped for under the conditions.

In 1917 a General Order forbade the use of cameras in the A. E. F. by anyone except the Signal Corps. In March, 1918, an elaborate schedule

\* Abstract of chapter written for the History of the Medical Department, United States Army.

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for the taking of photographs by the Signal Corps to be used to illustrate the Medical History of the war was approved by the Chief Surgeon of the A. E. F. In order to provide for the taking of technical photographs other than those to be used in illustrating the medical history, request was made early in May for the privilege of cabling for photographers and artists who were then in readiness to proceed from the Army Medical Museum in Washington. Approval of this request was refused by the General Staff "in view of the existing tonnage situation." The General Staff's endorsement further stated: "In this connection, it is believed that the requirements of the Medical Corps may be successfully met in this particular by the personnel and facilities already here in both the Signal and Engineer Corps." The lack of men with special training in medical illustrating in the Signal and Engineer Corps and the necessity for this special training for the production of good work were pointed out in another memorandum in July, and one officer and seven enlisted men, specially trained artists, were cabled for and arrived in France Sept. 14, 1918.

May 5, 1918, General Order 78 amended previous orders and gave to the Medical Department authority to make "technical photographs of surgical and pathological interest." A survey was made of the Medical Department personnel in the A. E. F. and several photographers were found with training in the taking of photographs of medical subjects. Owing, however, to the order previously issued forbidding the taking of photographs, almost no hospitals were equipped with cameras or other photographic apparatus. Those that were so equipped were authorized to place their apparatus in use. A few cameras were available from French sources, three were borrowed from the Signal Corps, and twenty-four from the Roentgenologic Department. A limited amount of photographic supplies was obtained from French sources.

A survey of the feasible sources of supply, American, French and British, revealed the fact that nothing but formalin was obtainable for fixation of pathologic specimens except that a few base hospitals first to arrive in France had brought over with them a small supply of alcohol. The only materials available for color preservation were sodium or potassium acetate and nitrate, one or the other of which was obtained after long delay from French sources. These materials, photographic and pathologic, were placed in the Central Medical Supply depot, where they suffered along with other medical supplies from inadequate facilities for distribution.



After a careful survey of the situation, Circular No 42 was issued, of which the following is an abstract:

AMERICAN EXPEDITIONARY FORCES

CIRCULAR No. 42.

France, 27th July, 1918.

COLLECTION OF MUSEUM MATERIAL FOR MEDICAL EDUCATION AND RESEARCH

1. *Object.*—This circular is for the information of those branches of the service whose cooperation and assistance are necessary to enable the Army Medical Museum to discharge its duty of collecting all those things which may be used for medical education and research or which may be of historical interest. This material will consist of pathological specimens, bacteria, animal parasites, missiles, armor, instruments, apparatus, casts, models, paintings, drawings, diagrams, charts, statistical tables, cinema films, photographs, radiographs, lantern slides or other things pertaining to the preservation of the health and the prevention and treatment of the diseases of the United States soldiers or to the history of the Medical Department of the Army.

2. *Scope.*—In France all collections will be limited to those things which can not be obtained readily in the United States or which are necessary for study in the A.E.F. More specifically these will relate principally to war wounds, especially lesions of the bones and vital organs, gas poisoning, trench foot, gas gangrene, traumatic and shell shock, to infections and parasitic diseases of special menace to the A.E.F. and to material of historic interest. Other material may be included if obviously desirable.

3. *Responsibility.*—It is the duty of each medical officer in the A.E.F. to direct into proper channels all such desirable material coming to his notice. In each medical unit the pathologist, or in his absence some other medical officer, will be responsible for the collection, preservation and shipment of all such material obtainable in the unit.

4. *Use in A.E.F.*—Collected material required for investigation in the A.E.F. will be shipped as early and as directly as possible to the groups of officers conducting the investigations in such manner and quantity as they may request.

. . . . .

After serving the needs of the immediate investigation the material, if still of value, will be preserved.

. . . . .

5. *Concentration points*.—All other collected material will be shipped without unnecessary delay to concentration points (Headquarters Laboratory Division, Base Laboratories, Base Sections, etc).

. . . . .

6. *Final disposition*.—At the concentration points the Museum Unit will take charge of the future preparation of all material and its shipment to the Army Medical Museum.

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7. *Pathological specimens*.—(Detailed directions for fixation and preservation.)

. . . . .

8. *Shipment*.—When pathological specimens have been fixed for two weeks or more they should be well padded with absorbent cotton, wetted with the solution in which they have been last immersed, and then wrapped in water proof paper (to be obtained by requisition) and packed with paper, excelsior, hay or similar material in a strong wooden or tin box or barrel and shipped to the most accessible point of concentration. . . . .

9. *Bacteria*.— . . . .

10. *Microscopic slides*.— . . . .

11. *Animal parasites*.— . . . .

12. *Missiles*.—For the psychic effect a missile removed from the body of a wounded soldier may be given to him if he wishes to keep it. However, he may be induced to relinquish his claim when the scientific value of a comparative study of such missiles and their preservation in a museum is explained to him. The place and character of all missiles in amputation material should at least be accurately described, and, if possible, sketched. All missiles and foreign bodies removed at autopsies should be carefully preserved, if possible in situ, with the pathological specimen. When it is necessary to remove them, their location and wound effects should be minutely described, the description, if possible, being accompanied by photographs or sketches.

13. *Armor*.—Armor, such as helmets, or other protective body covering showing the effects of missiles, gases, etc., should whenever obtainable be preserved with full data concerning the incidents of their use. . . . .

14. *Instruments and apparatus*.—All instruments and apparatus of special value which have been developed or materially modified in

the A. E. F. should be photographed, accurately described, and if it seems desirable models made.

. . . . .

15. *Casts and models.*—The number of skilled casts and model makers in the A. E. F. is extremely limited. When a medical officer has some specimen or series of specimens or cases, showing results of operations which he wishes to have illustrated in wax or plaster he should make application . . . . . for the services of a model maker.

16. *Painting, drawings, diagrams.*—It is believed that in many hospitals there may be found men capable of making diagrams, sketches, furnishing graphic records of teaching or historic value to the Medical Department. Well-trained medical illustrators, on the other hand, are scarce, and their services, to be utilized in an economical manner, must be centrally controlled. . . . .

17. *Cinema films.*— . . . . .

18. *Photographs.*— . . . . .

19. *Radiographs.*— . . . . .

20. *Original publication.*—All pathological specimens, casts, models, paintings, drawings, photographs, radiograms, etc., should be accompanied by the name of the medical officer collecting them and of the medical officers, if any, specially interested in their subject matter. This is important not only for the occasional necessity of retracing them back to their origin for additional data, but also that the privilege of original publication of the data by the officer with whom they originated may be respected.

21. *Supplies.*— . . . . .

M. W. Ireland  
Brig. Gen., M.C., N.A.,  
Chief Surgeon

As a result of the preliminary work above described, the increase in the total number of morbid anatomists and the placing of them at advantageous points and of personal appeals while inspecting laboratories, a considerable interest in the collection of museum material was developed. The battle activities in June and July, however, so overwhelmed the Laboratory Division, as well as other divisions of the Medical Department, that very few collections of pathologic

specimens were made; the pathologists, still most discouragingly lacking in numbers, were hopelessly overworked, and very rightly gave their attention to rendering information to the attending medical and surgical officers which could be of immediate service with the sick and wounded in as many cases as possible rather than to collecting pathologic material for scientific study in the future. In October and November the epidemic of influenza, coinciding as it did with the Argonne offensive, the period of greatest battle activity in the A. E. F. equally overwhelmed the pathologists, though by this time their number had materially increased. During this period an excellent necropsy service had been developed, but attention could be given in only a minor degree to the collection of specimens. Nevertheless, despite the limited personnel, and, the lack of equipment, of supplies, of containers, of transportation, of time, and in fact of everything except an avalanche of tissues, upwards of six thousand pathologic specimens were collected, preserved, and shipped to the Army Medical Museum.

These specimens for the most part illustrate the principal groups indicated in Circular No. 42 and relate chiefly to war wounds and gas poisoning. Early lesions of war gas poisoning were especially difficult to obtain owing to lack of transportation or pathologists and to the necessity for the centralization of specimens for immediate study at the pathologic laboratory in the Chemical Warfare Service with which the Medical Department attempted to cooperate in every possible manner. However, a small but a fairly representative collection of those lesions was obtained. A number of good specimens illustrating the more striking types of lung lesions occurring during the epidemic of influenza in the fall of 1918 were preserved. Lesions illustrating the often unique course of typhoid and paratyphoid fever in vaccinated men were also collected in considerable numbers during the fall and winter of 1918-1919. In addition a fairly good collection of brain and cord and peripheral nerve lesions of congenital anomalies, and so forth, was made.

The collection of about 2000 selected microscopic slides of tissue was shipped to the United States.

A small collection of missiles which had caused injuries and which had been removed at surgical operations was preserved. Most of these missiles were, however, according to the instructions in Circular No. 42, returned to the wounded soldier. A fairly complete collection

of unused small arms missiles and fixed ammunition of the various warring nations, together with a few specimens of heavy ordnance missiles and fragments thereof was forwarded to the Army Medical Museum.

A representative collection of rifles, pistols, bayonettes, trench knives and other weapons directly concerned in the making of wounds was forwarded to the Army Medical Museum.

A large collection of helmets, which showed evidence of having been hit by missiles which they had either warded off or had been penetrated by, together with a small number of pieces of body armor and metal objects such as canteens, messkits, trench mirrors, and so forth, which similarly had been struck by missiles was collected and shipped to the Museum.

A number of medical and surgical instruments and pieces of apparatus of American, ally or enemy origin which had been developed or materially modified during the progress of the war were collected and shipped to the Army Medical Museum.

Several artists (medical illustrators, wax modelers, and others) arrived in France attached to Base Hospital No. 115, which was stationed at Vichy, in September, 1918. An art and photographic section was therefore established in Vichy in the Central Laboratory of the Base Hospital Center, using this personnel and its equipment. Other artists were assigned from time to time to the work in this art section and were ordered out therefrom to various hospitals in the A. E. F. where medical illustrating was needed. This group produced 35 casts of surgical cases, about 200 drawings and paintings and more than 1,000 photographs of technical subjects. In addition to these illustrations and photographs of technical subjects centered at Vichy a number of other drawings, paintings, and photographs of technical subjects were made in other centers, particularly at Allerey, Beaune, Chateauroux, and Paris.

The cinema camerist, photographers, and artists cabled for in August, as mentioned above, reported for duty to the Director of Laboratories September 14. This personnel was distributed as advantageously as possible, principally to cover the activities of combat divisions. Here they remained on duty until the signing of the armistice. Late in September, 1918, the Museum Section of the Division of Laboratories had been charged with the duty of cooperating with the Signal Corps in the making of photographs for the Medical

**History of the War.** The Signal Corps, though it had been authorized in March, 1918, to prepare such photographs, had been able to cover but little of the medical activities of the A. E. F. except the more popular subjects which were needed for propaganda purposes. After the signing of the armistice and as soon as the general photographers of the Medical Department could be released from their duties with combat divisions a Photographic Bureau of the Medical Department was established in Paris for the making and collecting, both with Medical Department personnel and the Signal Corps personnel, photographs and moving pictures illustrating the Medical History of the War. The negatives of the medical pictures taken by the Signal Corps photographers were developed by them and two prints of each made for the Medical Department Bureau, the negative being retained by the Medical Corps. The negatives made by medical personnel were developed, printed, and filed in the Medical Department Bureau. This bureau filed more than 10,000 still pictures, titled and cross indexed. It supplied about 5,000 proof copies to hospital organizations for use in their several histories and 1,500 prints for medical officers of the General Staff of G. H. Q. The bureau also photographed about 350 dental specimens. It has made about 40,000 feet of moving picture film of surgical and medical subjects, such as activities in and around hospitals, convalescent patients, and psychiatric cases. In addition it filed about 20,000 feet of motion pictures made by Signal Corps photographers. Nineteen copies of the motion picture "Fit to fight" were made for circulation in the A. E. F. Two other propaganda pictures—"Fit for America" and "How to avoid typhoid fever"—and six copies of a two-reel anatomic venereal picture were also made.

The Radiographic Division on request from the Division of Laboratories packed and shipped about 2,000 selected x-ray plates from their point of origin directly to the Army Medical Museum. These were selected for their technical quality as well as for their scientific interest and cover in a number of instances special series of cases or series showing different stages in the treatment and healing of the same case.

Immediately on the signing of the armistice, it became obvious that transportation facilities for specimens, not only within the A. E. F. but also from base ports to the United States, would be exceedingly limited. A supplemental museum circular was therefore issued from the Chief Surgeon's office giving directions for expediting transportation and calling attention to the desirability of obtaining material

showing stages of healing. As a result of this circular the transportation of pathologic specimens directly to base ports from their points of origin instead of through collection centers was materially expedited though it resulted in having to depend on a large number of shippers for details concerning the individual specimens and consequent lack of detailed information in some instances. Shipment of museum material to the United States was greatly hampered by the confusion incident to general shipping conditions in France and to the lack of tonnage at the close of the war. All the specimens, however, were carefully packed, and it is believed they will not materially deteriorate even if delayed one or two years in transit.

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In planning for the future collection of material for the Army Medical Museum a definite policy should be clearly stated and adhered to. This should be based on the principle that such collections are primarily for purposes of education and research and only remotely of historic interest. Important historical material is rare, isolated and difficult of recognition. That which is too often selected is only of curious interest and in a little while becomes museum junk. A brief Army Medical Museum Manual which should clearly define the objects of the museum collections, state in detail the material desired and why, and give directions for simple methods of collecting, preserving, and shipping specimens, if widely circulated in the Medical Corps and among physicians, especially laboratory men in civil practice, would go far toward developing the proper conception of Medical Museums and greatly improve the character as well as increase the quantity of the collections. The cooperation of the Association of International Medical Museums might well be sought in planning such a manual.

In plans for future expeditionary forces of the United States Army it is suggested that the collection of the material for the Army Medical Museum be made a part of the duties of the Division of Laboratories. This division should also be charged with the duty of making, collecting, and forwarding moving pictures, photographs, drawings, paintings, models, etc., representing the administrative, general, and technical activities of the Medical Department in all its aspects. These photographs, if collected by previously prepared personnel and the supervision made the definite duty of every laboratory officer, would be of

inestimable value from both the historical and scientific standpoints. Restrictions on photography, such as operated early in the history of the A. E. F. so greatly to hamper the activities of the Medical Department would seem to be unnecessary for safeguarding information, the Laboratory Division no doubt being as trustworthy as the Signal Corps. Preparation should be made in peace times for the selection of trained personnel for the various highly specialized functions which must necessarily be performed. Provision should also be made for a standard photographic equipment to be supplied to the laboratories of various types. Special attention should be paid to photographs of methods of handling the wounded and of the appearance and treatment of battle injuries in forward areas, an adequate knowledge of the conditions of which is so essential and yet so difficult to convey to the inexperienced medical officer.



## GRADUATE MEDICAL EDUCATION IN GREAT BRITAIN AND FRANCE\*

L. B. WILSON

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At the meeting of the Executive Committee of the Council on Medical Education of the American Medical Association Feb. 3, 1918, the Committee on Graduate Medical Degrees appointed the previous year was continued, and its duties enlarged to include a study of the entire problem of graduate medical instruction in this country and in the countries of our allies. The personnel of the Committee is as follows: Louis B. Wilson, Chairman; N. P. Colwell, Secretary; Isadore Dyer; John M. Dodson; A. C. Eycleshymer; William Pepper, Jr. Victor C. Vaughan; J. M. T. Finney; Edward Jackson; and James Ewing.

The Chairman of the Committee was instructed, should he be ordered to military duty in Europe, to make such observations and collect such information concerning graduate medical education there as time and opportunity would permit. It so happened that he was stationed in London during April, 1918, and in France from April, 1918, to June, 1919, except for a brief visit again to England in April, 1919. During this time he had conferences with Sir William Osler, Chairman of a committee representing the London Medical Schools; with Sir George Makins, Professor Arthur Keith and Sir Arbuthnot Lane of London; Sir Berkeley Moynihan of Leeds; Sir Robert Jones of Liverpool; Sir Harold Stiles and Sir William McCormack of Edinburgh; Colonel J. W. Adami of the Canadian Medical Service, and with Sir Walter Morley Fletcher of the Medical Research Committee. In France similar conferences were held with Professor Henri Roger, Dean of the Faculty of Medicine, University of Paris; M. Georges Destouches, Secretary of the Faculty; Dr. Calmette, one of the Directors of the Pasteur Institute; Dr. A. Bécclère, President of the Association Médical des Hôpitaux de Paris; Professor A. Policard of the Lyon Medical School, and with numerous other French medical officers met incidentally. Conferences were also held with Dr. George H. Nettleton, Director of the American university Union in Europe, and Dr. George E. MacLean, Acting Director of the British branch of the American University

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Union. No opportunity was afforded for the study of the graduate medical situation in Italy although incidental information would indicate that in certain of the schools there are opportunities for Americans to work to advantage, particularly in laboratory subjects. The results of the observations in Great Britain and France are herewith presented as an interim report in the hope that the information may be of use to some of the many Americans now seeking opportunity for graduate medical study.

*Great Britain.*—The numerous three-months courses in medicine which were attended by about 300 medical officers of the American Expeditionary Forces after the armistice furnished many suggestions to the instructors, particularly in the London and Edinburgh medical schools, concerning the kind of work desired by American graduate medical students. They also demonstrated to American medical students the high quality of work to be had even under the adverse conditions then obtaining. On the basis of this experience Sir William Osler's committee has formulated, with the cooperation of the twelve London undergraduate medical schools, the four existing postgraduate institutions, and many hospitals, a plan for lectures in the fundamental medical subjects, clinical teaching in cases in wards and out-patient departments, practical instruction in x-ray diagnosis, pathologic chemistry, bacteriology, clinical microscopy, postmortems, and so forth. The cooperation of the British medical schools outside of London will probably soon be secured. Special research work and clinical assistantships are also available to qualified men. Many of these courses will be most excellent, and American graduates in medicine will greatly appreciate them.

The central organization consists of a Council made up of representatives of all the participating teaching institutions and representatives of the Board of Education, the Medical Research Committee, the Dominions, and American universities. This governing body assists in the organization of courses, maintains a uniformity of fees in the various schools, and furnishes detailed information concerning courses. Ultimately the Association will have a building in central London not only containing offices of the organization but also forming a meeting place for medical graduates of the Empire and allied nations. American students desiring detailed information concerning the courses available should correspond with the Director of the American University Union, 16 Pall Mall, East, S.W. I., London.

Recently a union has been accomplished between the Osler group for graduate study and the American Hospital of London. This latter institution, which was developed largely through the activities of Sir Arbuthnot Lane, has the financial support of a number of influential Americans and Englishmen in London. It is proposed to build a large hospital well equipped not only for the care of patients but also for clinical teaching and laboratory research work. The patients may be derived from any available source. The attending medical officers will be recruited from among the most eminent of the London members of the medical profession while the house officers, interns, and graduate students will be made up of Americans. Anyone desiring information concerning the opportunities offered in this hospital should inquire of Mr. Phillip Franklin, No. 1 Wimpole St. S. 1, London.

Information at present is not at hand concerning the graduate courses in medicine actually open to American medical students in the British medical schools outside of London. It is known, however, that there are such opportunities, particularly at Edinburgh and Liverpool. Information concerning these may be obtained direct from the secretaries of the faculties.

American medical students, of course, will find very great variation in the kind and quality of the teaching by the individual instructors in Great Britain. In general, however, they may expect to find the British medical man a thoroughly trained clinician, a sturdy advocate of the unvarnished truth, not taking kindly to unsupported hypotheses, without much reverence for supposedly established medical "authorities," and in criticism likely to "hew to the line, let the chips fly where they may." His personal atmosphere contains no "London fog," and is delightfully bracing.

*France.*—In France, although all medical education is under the general control of the Minister of Education, each medical school has its own peculiarly individual plan of work. During the war the French medical schools were almost completely disorganized, but they have made rapid progress at reorganization since the armistice. Perhaps the graduate work most readily available to American medical students in France at present is that offered by the Association de Hôpitaux de Paris, of which Dr. A. Bécère, 122 Rue la Boétie, is president. This organization, which was formed in 1907, contains a large number of the most prominent physicians, surgeons, and spe-

cialists in Paris who have associated themselves together for the better utilization for teaching purposes of the clinical material which they control in the various hospitals. The courses offered by the different members of the association are announced annually in a bulletin which may be obtained from the president of the association. Whatever divergence of interests may have previously existed between the teachers of this association and the school of Medicine of the University of Paris has now been corrected and the two are working together in harmony for the development of graduate medical education.

In cooperation with these French organizations is the American University Union in Paris and the "College of the United States of America." Mr. George H. Nettleton, Director of the American University Union, Paris, during the war interested himself not only in the purpose for which the American University Union was primarily formed, that is, "to meet the need of American university and college men and their friends who are in Europe for military or other service in the cause of the allies," but also in the promotion of a broad basis of better relationships between the educational interests of the United States and France. Through M. André Tardieu, Commissaire General des Affaires de Guerre Franco-Américaines, and M. Coville, Director of Higher Education, he did much to bring about an understanding of the need of American university students and of what the United States has to offer to French university students. The American University Union has been given a grant of land in Paris on which to place a building for its general headquarters. Funds for the erection of such a building are now being obtained. This building will no doubt become a general meeting point and source of information for University students in France. Graduate medical students desiring information concerning the courses available should correspond directly with the American University Union at 8 Rue de Richelieu, Paris.

"The College of the United States of America," which is incorporated under the laws of the States of West Virginia, with its principal office at 24 Boulevard des Capuchines, is supported by a number of wealthy Americans resident in Paris. It announces that "the object of this organization is to create in Paris an institution of learning to promote intellectual rapprochement between France and the United States, to constitute a clearing house for the exchange, discussion and dissemination of ideas in all the various branches of education, science

and learning, and finally to constitute a sort of administrative home for students in France. It proposes by way of beginning to establish immediately in Paris an office or bureau as the headquarters of the new institution where may be found a complete list of the teaching facilities of France with the names of all the well known savants willing to accept graduate students in their classes, clinics and laboratories."

Outside of Paris probably the best opportunities for graduate study of medicine in France will be found at the Medical Schools of Lyon, Lille, and Strashurg. All of these are in the process of reorganization and will soon be able to offer good opportunities for graduate study.

An American graduate medical student who has command of the French language will find study in France most inspiring. The Frenchman has none of the wearying, plodding methods of the Teuton, but he arrives at his conclusions across lots, apparently by intuition, actually by the subconscious guidance of wide clinical experience and a wonderfully clear mental vision, which is a racial characteristic.

French university undergraduate medical teaching in some places has not materially advanced since the days of Louis, Oliver Wendell Holmes' great instructor, but the Frenchman is an intense individualist, and the American medical student who seeks inspiration in almost any clinical specialty or in research by search can find some great teacher in France who is sure to give him a new and original point of view. Mention may be made of the special excellence of French work in the roentgen ray, diseases of the nervous system, skin and venereal diseases, and ophthalmology.

*Expenses.*—The expenses of American graduate medical students in England and France, except for the ocean travel, should not be materially greater than in the United States. It is to be hoped that endowed traveling fellowships for study in these countries, paying at least as high a stipend as those provided for graduate medical study in the United States may soon be greatly increased in number.

*The Institute of international education.*—This article would be incomplete without mention of the Institute of International Education, 421 West 117th St., New York City, under the patronage of the Carnegie Foundation, which is now promoting an extensive plan of exchange of instructors between the United States and allied countries and which later I believe expects to develop a similar plan for the exchange of students.

## MEMORIAL MEETING IN HONOR OF SIR WILLIAM OSLER\*

Sir William Osler died at his home at 13 Norham Gardens, Oxford, England, late Monday evening, December 29.

A memorial meeting in his honor was held by the staff of the Mayo Clinic Wednesday evening, December 31, in the Lobby of the Clinic building. The following are abstracts of addresses made by the several speakers:

*Dr. Herbert Z. Giffin:*

"Sir William Osler whose death we mourn possessed an appeal for every type of medical man, because of the versatility of his nature. He is well known to us as a scholar of the classics, as a medical philosopher, and as a collector of rare books. Dr. Osler's scholarly tendencies made him no less a man of action. He was able to accomplish an enormous amount of work because he spent no more time on one thing than was necessary to a thorough completion of the task.

"My association with Dr. Osler has been in the role of pupil, for a period of two years as a student, and one year as an intern. His characteristics are clearly before me. His striking attitudes and gestures created a certain physical charm as they were absolutely lacking in affectation. Dr. Osler's humor was subtle and unexpected, and his manner of expression epigrammatic. Many of his remarks were indelibly impressed on the minds of his hearers because of their originality.

"As a medical man Dr. Osler was first a pathologist. In demonstrating cases he led the student to develop a complete classification of related conditions so that a mental view of wide scope was obtained. Dr. Osler's tolerance and patience with his students was one of his most notable characteristics. There was manifest no chiding spirit in his nature which was filled with 'the milk of human kindness.'"

*Dr. William C. MacCarty:*

"I can speak of Dr. Osler merely as I saw him during four years as his pupil, as I saw him again at a German Congress in München, as

\* Reprinted from The Clinic Bulletin, 1920 (Jan. 6.), i, No. 131.

I have seen him through his writings, and as I have had time to analyze his characteristics as a great physician, teacher, and factor in civilization. Like all of his students I was impressed by his thoroughness in investigation, simplicity of method in teaching, his humanitarian spirit toward patient and student, his charity for all mankind, and his inspiring and hopefully sane philosophy of life. He was perhaps the greatest correlator of the facts of pathology with clinical facts and represented the ideal evolution of a great teacher; the long student and research periods preparatory to practice were well exemplified in his own life. He taught and lived this ideal. He kept young and made progress to the last by 'changing his pasture.'

"In medical congress Dr. Osler lost none of the characteristics seen by the student. Surrounded by admiring and perhaps almost worshipping elder members of the medical profession he was still the same Dr. Osler by which title he will ever be remembered by his American students, not because we do not enjoy seeing him with the title of 'Sir' but because our great affection for him reaches its zenith when we speak of 'Dr.' Osler.

His type of mind, it seems to me, belonged to the "Romantiker," Wilhelm Ostwald having classified minds of great men into two groups, that is, 'die Klassiker' and 'die Romantiker,' the first characterized by slowness of observation, correlation, generalization and utilization, the second by rapidity of action of these qualities. Dr. Osler was of the latter type, a type which produces great reformers; men who mark epochs by their generalization in utterances and writings; men who defy traditions not in keeping with new facts.

"It was he who reduced the size of the pharmacopoea; it was he who relegated the ridiculously long and meaningless prescription to the graveyard for witchcraft, sorcery, superstition, and charlatanism; it was he who taught us bedside teaching in America.

"Dr. Osler's keen appreciation of the practical value of the classics and his constructive criticism of them as utilized and taught by classical scholars of today is well shown in his address before the Classical Association of Oxford under the title 'The Old Humanities and the New Science.'

"To us Dr. Osler is not dead—he lives for us as the spirit of our greatest teacher, physician, philosopher, and soldiers' aid, and represents the acme of Anglo-Saxon, if not indeed human, heroism in peace and war. His own deepest of human suffering he subordinated

to the noble spirit of altruistic humanism. Brutal revenge which has reached its most diabolical efficiency in the thought and actions of man had no place in his, the highest type of civilized activity.

"It is left for us, his disciples, to live and act daily as he would have us to live and act. This, I am sure, would give him the greatest pleasure were he here."

*Dr. Louis B. Wilson:*

"All of us are familiar with Osler as a great teacher of medicine. I wish to speak briefly of him as a man and especially of his work during the world war.

"Besides making hospital rounds and engaging in medical consultation many hours a day—services in which his great experience and ripe judgment were of incalculable value—his advice and counsel were constantly sought and always freely obtained on the thousand and one serious problems which confronted the British medical profession during the war. Early in 1918, as chairman of the committee of representatives from the various medical schools of England, he began the organization of these institutions to care for graduate medical instruction after the war, and just before being taken ill was about to see the fruition of his plans in the coordination of this work in a central building in London.

"Shortly after being ordered to London in April, 1918, I wrote Osler concerning graduate medical work and was immediately invited down to Oxford for the week-end. The last sentence in his note, 'If you have been in London long enough to have a meat ticket, bring one,' suggests the state of England at that time—a time when Haig had just made his famous address 'With our backs to the wall,' and suggests how great a boon such an invitation to Osler's beautiful home was to any American army officer in 'Base Section 3.' This privilege of enjoying the unsurpassed hospitality of Sir William and Lady Osler was extended by them to over 1500 Canadians and Americans during the war. After the death of their son, instead of shutting themselves in with their terrible grief, they continued to make their home a mecca for all Canadians and Americans, a real oasis in the desert of routine military life. How he and Lady Osler thus hid their sorrow and used their home and their odd moments to give pleasure to homesick men and women is to me one of the most beautiful and touching incidents of the war.



"When I visited Oxford again in April, 1919, Osler, like everyone else, seemed to be a bit weary after the long war strain, but the relaxation did not, as it did with others, disturb his mental poise, his equanimity. Aside from his routine medical duties, which still were heavy, he had plunged more deeply into the organization of medical graduate work and in addition was keenly anticipating going on with his work on medical bibliography. Perhaps no man ever had a fuller and better balanced enjoyment of the insides as well as of the outsides of books than had Osler. His house was filled with them and the great Bodleian Library was at his mental finger tips. His bibliography of medicine, arranged by subjects in which the literature is classified as of primary and secondary importance, when published will no doubt prove to be one of the clearest and most faithful analyses of the development of a science that has ever been made.

"Osler retained throughout the terrible weariness of the war his wonderful teaching power, his facile skill in fixing a scientific truth by some never-to-be-forgotten quip or jest; his kindliness to the patients and to his house officers, his policy of attending all autopsies on his patients, and his clear insight into the new things in medical science. But it was more especially in his geniality, in his great love for little children, in his real human interest in the affairs of the many young officers invited to his home, in his broad philosophy, in his wide learning in all those fields pertaining even most remotely to medicine, and in his knowledge of and interest in national policies and international relationships, particularly of Great Britain and her overseas possessions with the United States and France, that one was impressed with the sweetness as well as the bigness of his matured powers. He was not only one of the greatest teachers of medicine and one of the most lovable of men but he had also one of the biggest minds this world has ever known."

*Dr. William J. Mayo:*

"In the death of Sir William Osler a great man has passed out of the medical world. No one of his generation did more to advance medical education, and research, and to diffuse medical knowledge than Dr. Osler. As a teacher he was enthusiastic, logical, and above all, inspiring. Those who had the pleasure of listening to him were made better not only by the tangible things he presented, but even more by the intangible, which led to a higher consciousness of duty to the patient, to the public, and to science. His textbook on the practice of

medicine is concise and clear, it deals with facts and is suggestive rather than didactic in treatment. Through its successive editions it has been the daily handbook of the English speaking physician for thirty years. As I look over these volumes, and as I remember the kindness of the man, his interest in medicine as a whole, and in medical men low and high, I realize only too well what Dr. Osler meant not to the few but to the many.

"Sir William Osler came from Canada to the United States with a mission of friendship between two American countries separated only by an imaginary line. He went from us to England, with a mission as our advocate in the great British councils, carrying with him the affection of the Americans as a whole. He had a fine spirit of patriotism, yet a patriotism which was not English, and not American, but was based on a complete understanding and love for the English speaking people. The influence of such men as Osler was shown in the response of the United States to the cause of the allies in the great war.

"In the death of Sir William Osler the clinic has lost a friend. Every year various members of the staff of the clinic have received personal letters from him, in his own handwriting, expressing his appreciation, breathing encouragement to loftier purposes and ideals. Occasionally, as he visited around the world, medical mementos of his travel came to us as evidence of his thought, some of which you will find hanging in the halls of this building. The life of Dr. Osler is an inspiration and an example for medical men. As a teacher, an author, and as a man, can anyone name his equal in the last generation? I cannot."

*Dr. Charles H. Mayo:*

"Humanity has sustained a great loss in the death of Sir William Osler. By reason of his extensive general knowledge and interest in varied scientific development he became widely known, and his loss is most keenly felt by those whose knowledge of medicine enables them to appreciate the great part he played in its development as a writer and teacher. During the allotted span of life which he reached he became a learned and constant contributor to the world's scientific progress. Reading his 'Practice' after those which had preceded it is like opening a window in a close room. Canada, the land of his birth, has ever been proud of her illustrious son, and his early work there laid the foundation for much of the development of medical

education in that country. The United States was proud to own him in that period of growth of the knowledge of the cause of disease, in association with its pathology, which Dr. Osler did more to develop as a fundamental basis of medicine than any other man of his period. To be appreciated and mourned by the profession as Dr. Osler is in both the old and new world is a rare recognition and is accorded to but few representatives of the profession. To know Dr. Osler personally added to the joy of life."

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